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Thesis for the Degree of Doctor of Philosophy

Effect of circadian rhythm and exercise order on obesity-related cardiovascular disease risk factors, upper and lower extremity muscle functions and skeletal muscle metabolism

Yeong-Hyun Cho

Department of Kinesiology

GRADUATE SCHOOL

JEJU NATIONAL UNIVERSITY

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Effect of circadian rhythm and exercise order on obesity-related cardiovascular disease risk factors, upper and lower extremity muscle functions and skeletal muscle metabolism

Yeong-Hyun Cho

(Supervised by Professor Tae-Beom Seo)

A thesis submitted in partial fulfillment of the requirement for the degree of
DOCTOR OF KINESIOLOGY

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Abstract

Effect of circadian rhythm and exercise order on obesity-related cardiovascular disease risk factors, upper and lower extremity muscle functions and skeletal muscle metabolism

Yeong-Hyun Cho

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Graduate school of Jeju National University

Jeju, Korea

(Supervised by professor Tae-Beom Seo)

The purpose of this study was to determine the effect of combined exercise program according to circadian rhythm and exercise order on cardiovascular disease risk factors, upper and low extremity muscle functions, and skeletal muscle metabolism in human and animals with obesity. This study consists of two experiments, one is a clinical trial targeting obese women (study Ⅰ) and the other is animal experiment using obese rats (study Ⅱ).

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In study Ⅰ, we determined the effect of combined exercise program according to circadian rhythm and exercise order on body composition, cardiovascular disease risk factors, skeletal muscle functions and sleep quality in obese women. Fifty five women were recruited to participate in this study, and five participants who did not meet the target selection criteria (be ruled out body fat percentage <30%, definitely morning and evening type) were excluded. Fifty obese women were randomly assigned to each group. During the experiment, six participants were excluded according to personal reasons and exercise participation rate criteria (80% or less). Finally, 44 obese women took part in the analysis of this study. All subjects were divided into 5 groups; the obesity control group (OCG, n=10), aerobic-resistance exercise in the morning group (MARG, n=8), resistance-aerobic exercise in the morning group (MRAG, n=9), aerobic-resistance exercise in the evening group (EARG, n=8), resistance-aerobic exercise in the evening group (ERAG, n=9). Combined exercise program consisted of treadmill exercise (30 min) and weight training (30 min) 3 days per week for 8 weeks. To investigate the effect of combined exercise program according to circadian rhythm and exercise order, body composition, physical fitness, obesity-related cardiovascular disease risk factors, upper and lower extremity muscle functions were analyzed previous, 4 and 8 weeks after the experiment. Significant differences between group and period were determined with two-way repeated ANOVA. And differences between groups were analyzed performing a one-way ANOVA followed by Scheffe *post-hoc* test. As the result of this study, combined exercise program did not significantly result in a change in body weight and body composition, but, this program showed positive changes in all exercise groups. The muscular strength, flexibility, cardiorespiratory endurance were no significant difference between group and periods, but muscular endurance was significantly higher in EARG at 8 weeks compared to OCG. Obesity-related cardiovascular disease risk factors were no significant difference among all groups. Upper extremity muscle functions including front and side abdominal power test did not show a significant interaction between group and periods. trunk flexor endurance

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test was significantly higher in EARG at 8 weeks than in OCG. Sit to stand test was significantly higher in EARG at 8 weeks than in OCG between group and periods. Pittsburgh sleep quality index was significantly lower in all exercise groups at 8 weeks than in OCG. Our findings suggested new evidence that aerobic-resistance exercise order in evening might increase physical fitness such as muscular endurance, upper and lower extremity muscle functions in obesity women, as well as that sleep quality might be improved by performing regular exercise program regardless of exercise order and time.

The purpose of this second study was to determine the effect of combined exercise according to circadian rhythm and exercise order on the expression level of proteins related with muscle hypertrophy and mitochondrial biogenesis in flexor pollicis longus and soleus muscle of obese rats. The random assignment method was applied, and all experiment rats (n=30) divided into five groups; the obesity control group (OCG, n=6), aerobic-resistance exercise in the morning group (MARG, n=6), resistance-aerobic exercise in the morning group (MRAG, n=6), aerobic-resistance exercise in the evening group (EARG, n=6), resistance-aerobic exercise in the evening group (ERAG, n=6). Combined exercise program was performed at a treadmill exercise (30 min) and ladder climbing exercise (30 min) 3 days per week for 8 weeks. For evaluating cross-sectional area (CSA) of flexor pollicis longus muscle, we applied a double immunofluorescence staining technique. And gene expression of muscle hypertrophy and mitochondrial biogenesis-related factors was identified by western blot analysis. Differences between groups were analyzed performing a one-way ANOVA followed by Tukey *post-hoc* test. The CSA of the flexor pollicis longus was significantly increased in MARG, EARG, and ERAG than in OCG. Among the groups that showed positive change, EARG had the largest CSA of the flexor pollicis longus. Muscle hypertrophy-related proteins such as insulin like growth factor 1 (IGF-1), phosphoinositide 3-kinases (PI3K) and phosphorylated extracellular signal-regulated kinase 1/2 (p-ERK1/2) in the flexor pollicis longus were higher in EARG compared to those in the other groups. EARG dramatically

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upregulated expression levels of phosphorylated protein kinase B (p-Akt) and phosphorylated mammalian target of rapamycin (p-mTOR) 8 weeks after combined exercise compared to those in other groups. Mitochondrial biogenesis-related proteins as such phosphorylated AMP-activated protein kinase (p-AMPK) and Ca^{2+}/calmodulin-dependent protein kinase (CaMK) were meaningfully upregulated expression levels in the MRAG after 8-week combined exercise. Also, Peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α) was significantly increased in EARG and MRAG than other groups. Fat browning-related gene, FNDC5, in the soleus muscle was showed significantly difference between groups after combined exercise. Present findings provide new information that aerobic exercise followed by resistance exercise in evening might activate cell biological changes on muscle hypertrophy and resistance exercise followed by aerobic exercise in morning might regulate aerobic functions via increase of mitochondria biogenesis.

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I. Introduction

1. Research significance

Obesity is a lifestyle-related disease that is prevalent in industrialized society and the untact era. It causes diabetes, cardiovascular disease, arthritis, depression, and cancer, and has harmful health-related consequences (Expert panel member et al., 2014). Nam et al. (2020) demonstrated that the obesity rate in Korean females increased continuously between 2009 and 2018, suggesting a problem with female obesity. Complications caused by obesity are closely related to increased medical expenses and socioeconomic problems. As a result, obesity prevention and treatment is important for solving socioeconomic problems and preventing health-related complications. There are numerous therapeutic strategies such as diet control, drugs, and procedures; recently however, the possibility of using circadian rhythm as a therapeutic strategy to manage obesity has been highlighted. The word “circadian” is derived from a combination of the Latin words “circa” and “diem”, which mean “around” and “day” respectively, as the rotation of the earth causes environmental changes such as the light-dark cycle. The human clock is governed by the body rhythm in the suprachiasmatic nucleus (SCN), which is located in the hypothalamus of the human brain (Engin, 2017). These circadian rhythms are closely related to sleep, heart rate, stress, and metabolism. A high correlation between short sleep duration and obesity in adults was observed in previous studies that demonstrated that sleep-time restriction decreases the amount of physical activity and increases the nervous response to food intake (Bromley et al., 2012; Cappuccio et al., 2008; Sperry et al., 2015; St-Onge et al., 2014).

Exercise has been established through previous studies as the most economical and effective way to prevent and manage obesity. The circadian rhythm is also closely related to exercise. A previous study that confirmed the effect of exercise with

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respect to the circadian rhythm showed that the secretion of neurotransmitters was increased in the afternoon compared to that in the morning, and muscle function was significantly higher (Kim et al., 2015; Küüsmaa et al., 2016). Souissi et al. (2012) observed that anaerobic exercise capacity was higher in the afternoon than in the morning, and recommended exercising in the afternoon to improve exercise performance. Contrastingly, other studies have reported that exercise performed at 6:00 a.m. is more effective than when performed at 6:00 p.m. in terms of muscle activity and efficiency; however, it does not draw a clear relationship between the circadian rhythm, exercise performance, and muscle function (Bessot et al., 2007). Exercise has been known to increase the levels of the sleep hormone melatonin and improve sleep quality, and it has been reported that the sleep-wake cycle hormones cortisol and melatonin are regulated according to the circadian rhythm. A study by Yang et al. (2012) on middle-aged and older adults showed that exercising for 10 to 16 weeks improved sleep quality and reduced sleep latency, clarifying the relationship between exercise and sleep. However, exercise for 6 months does not affect the rapid eye movement (REM) sleep changes during the entire sleep duration; hence, it is necessary to reassess the effect of exercise on sleep quality (Netzer et al., 1997). Sleep is affected by a master circadian clock controlled by light, and changes in the clocks pertaining to the blood vessels, heart, and muscles affect cardiovascular function. Hemodynamic measurements taken with respect to the circadian rhythm could explain the relationship between sleep and cardiovascular disease; studies have reported low heart rate and blood pressure changes at night and high heart rate and blood pressure early in the morning (Chellappa et al., 2019; Scheer et al., 2010). Cardiovascular disease has a high mortality rate worldwide and is reported to be closely related to sleep (Martikainen et al., 2011; Silvani & Dampney, 2013). Therefore, it is necessary to confirm the effect of exercise, according to the circadian rhythm, to treat cardiovascular disease.

Exercise can be classified as aerobic and anaerobic according to the largely mobilized energy metabolism process, and aerobic exercise utilizes fat as the main

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energy source, supplying the required energy through fatty acid oxidation, and continuing physical activity for a certain period. Therefore, aerobic exercise promotes the accumulation of oxidized fatty acids in the body and improves cardiopulmonary function by increasing the maximum oxygen intake along with reducing body fat (Lundsgaaed et al., 2018). In previous studies, it was observed that aerobic exercise reduced the prevalence of metabolic syndromes and brought the blood lipid levels and blood pressure to normal levels; it was also reported to be effective in weight control by increasing the appetite-regulating hormone leptin and the sleep hormone melatonin (Cai et al., 2014; Mathunjwa et al., 2013; Tiryaki-Sonmez et al., 2013). However, a study found that aerobic exercise was effective only in improving cardiopulmonary function and reducing body fat; it did not increase bone density and muscle mass, suggesting that aerobic exercise may be unsuitable for musculoskeletal development (Karavirta et al., 2011; Lundberg et al., 2014).

Resistance exercise, a representative anaerobic exercise that improves muscle strength and mass, is being introduced as an essential exercise for individuals with obesity, and resistance exercise generates energy through the breakdown of muscle glycogen and glycogen during exercise. Resistance exercise induces muscle hypertrophy through repetitive muscle contraction, and is also known to be effective in increasing skeletal muscle mass. In addition, resistance exercise promotes the secretion of hormones such as testosterone, growth hormone, and insulin growth factor (IGF-1), thereby inducing muscle synthesis in the body. it has been reported to reduce the expression level of tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), and interleukin-6 (IL-6) to reduce immune function and inflammation (Macêdo Santiago et al., 2018; Welle et al., 2002). However, studies have reported that because resistance exercise does not use fat as an energy source, it is less effective for body fat and weight loss compared to aerobic exercise; therefore, a combination of aerobic and resistance exercise has been recommended (Schmitz et al., 2003).

Combined exercise was performed to obtain the benefits of both types of exercises. In particular, it was reported that when people with obesity performed combined

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exercise, their immune function was improved due to increased physical strength and reduced visceral fat and TNF-α (Park et al., 2015). Additionally, combined exercise is being introduced as an effective treatment method to prevent obesity and chronic diseases because it can help in attaining the optimum body composition and reduce the risks of developing cardiovascular and metabolic diseases (Schroeder et al., 2019). However, researchers began to question the order of performing the exercise in such a way that effectiveness can be maximized, and it became an interesting topic for researchers in the field of physical education. A previous study reported that performing aerobic exercise after resistance exercise significantly increased muscular endurance the levels of catecholamine, testosterone, and IGF-1, compared to when resistance exercise was performed after aerobic exercise (Rosa et al., 2015). When resistance exercise was performed after aerobic exercise, lower cortisol levels and higher excess post-exercise oxygen consumption (EPOC) were observed, whereas when aerobic exercise was performed after resistance exercise, the total energy consumption and fat burning levels were higher (Drummond et al., 2005). Current research results demonstrate that the effects of exercise differ according to the exercise order, and this is controversial. The studies reported so far are primarily human studies, which have limitations in explaining the problem of environmental control and the mechanism of skeletal muscle metabolism. Therefore, researchers have observed the mechanisms of mitochondria biogenesis and hypertrophy in skeletal muscle in relation to aerobic exercise, resistance exercise, and circadian rhythm using experimental animals (Duguez et al., 2002; Groenneback & Vissing, 2017)

Mitochondria are organelles that exist inside and between skeletal muscle fibers and play an important role in energy and metabolic functions. Mitochondria dysfunction increases reactive oxygen species (ROS), which causes muscle atrophy and decreased endurance, and adversely affects energy generation (Glance et al., 2015). In addition, decreased mitochondrial function is closely related to obesity, which induces oxidative stress, and increased ROS disrupts the Krebs cycle and the normal energy production system (Madamanchi & Runge, 2007). Many researchers recommend exercise to

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improve mitochondrial function, and endurance exercise is known to combat mitochondrial dysfunction and solve problems in energy generation systems that are caused by obesity. Performing endurance exercise increases the expression of cyclic adenosine monophosphate (cAMP), Ca^{2+}/calmodulin-dependent protein kinase (CaMK), AMP-activated protein kinase (AMPK), and p38 mitogen-activated protein kinase (p38-MAPK), which are involved in muscle mitochondrial transcription regulation (Hardie et al., 2012). In order to prevent and manage obesity, both resistance and aerobic exercise are equally important, and resistance exercise induces the hypertrophy of human skeletal muscles and improves its function. Previous studies have shown that resistance exercise induces muscle hypertrophy through an anabolic pathway that includes phosphoinositide 3-kinases (PI3K), protein kinase B (Akt), and mechanistic target of rapamycin (mTOR) (Kumar et al., 2009). Additionally, resistance exercise also increases the expression of the IGF-1 anabolic hormone, promoting increased satellite cell proliferation and differentiation in myofibrils (Yang & Goldspink, 2002). Previous studies on the exercise order performed using experimental animals have shown that aerobic exercise performed after resistance exercise increased the expression level of AMPK and had a negative effect on the activity of the mTOR complex 1 (mTORC1) expressed through resistance exercise (Atherton et al., 2005). In contrast, Ogasawara et al. (2014) reported that there was no exercise order-dependent difference in the level of Akt and mTOR phosphorylation, and these results do not provide clear information about the exercise order. However, researchers have doubted whether these effects are controlled by the effect of exercise time, and have conducted studies on circadian rhythm and skeletal muscle metabolism. Sato et al. (2019) studied the body fat accumulation for evening and morning exercise, and reported that evening exercise reduced body mass accumulation in rats fed with high-fat diets. In addition, a previous study reported that evening exercise was more effective compared to morning exercise in promoting high aerobic exercise capacity and controlling glucose level, proving that the effects of exercise varied according to the circadian rhythm (Ezagouri et al., 2019).

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Considering the previous studies, the physical changes being attributed to the exercise order are controversial, and there are very few studies confirming that exercise that is performed according to the circadian rhythm can help manage obesity. In addition, studies that confirmed the mechanisms of muscle hypertrophy and mitochondrial biogenesis using a combination of circadian rhythm and exercise order are very scarce. Thus, further research is required to confirm the effect of the circadian rhythm and exercise order.

2. Research purpose

The objectives of this study were as follows:

Study Ⅰ. To investigate the effects of 8 weeks of combined exercise according to circadian rhythm and exercise order on body composition, physical fitness, obesity-related cardiovascular disease risk factors, upper and lower extremity muscle functions, and sleep quality in adult women with obesity.

Study II. To determine the effect of 8 weeks of combined exercise according to circadian rhythm and exercise order on muscle hypertrophy, mitochondrial biogenesis, and muscle cross-sectional area changes in rats with obesity.

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3. Research hypothesis

The research hypothesis addressed in this dissertation were as follows:

Study Ⅰ

1) The 8-week long combined exercise program, which was designed with respect to the circadian rhythm and exercise order, was expected to affect the body composition and waist/hip circumference ratio in women with obesity.

2) The 8-week long combined exercise program, which was designed with respect to the circadian rhythm and exercise order, was expected to affect the physical fitness in women with obesity.

3) The 8-week long combined exercise program, which was designed with respect to the circadian rhythm and exercise order, was expected to affect the cardiovascular disease risk factors in women with obesity.

4) The 8-week long combined exercise program, which was designed with respect to the circadian rhythm and exercise order, was expected to affect the upper and lower extremity muscle functions in women with obesity.

5) The 8-week long combined exercise program, which was designed with respect to the circadian rhythm and exercise order, was expected to affect the sleep quality in women with obesity.

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Study Ⅱ

1) The 8-week long combined exercise program, which was designed with respect to the circadian rhythm and exercise order, was expected to affect the changes in body weight in rats with obesity.

2) The 8-week long combined exercise program, which was designed with respect to the circadian rhythm and exercise order, was expected to affect the changes in cross section area of flexor pollicis lingus muscle in rats with obesity.

3) The 8-week long combined exercise program, which was designed with respect to the circadian rhythm and exercise order, was expected to affect the changes in muscle hypertrophy-related proteins of flexor pollicis lingus muscle in rats with obesity.

4) The 8-week long combined exercise program, which was designed with respect to the circadian rhythm and exercise order, was expected to affect the changes in mitochondrial biogenesis related proteins of soleus muscle in rats with obesity.

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4. Research Limitations

The research limitations of this study were as follows:

1) The participant of the study was limited to a specific area.

2) The psychological factors of the study participants could not be controlled.

3) The diet, sleep time, and physiological phenomena of the study participants were not completely controlled.

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5. Operational definitions

The following definitions and explanations of the terms were established for use in this study:

1) Circadian rhythm

A change in the sleep-awakening cycle, hormones, body temperature, autonomic nervous system regulation, and metabolism every 24 hours.

2) Aerobic exercise

A form of exercise in which oxygen is mobilized to produce energy for performing continuous exercise.

3) Resistance exercise

An exercise method used to increase muscle hypertrophy and muscle strength, which does not mobilize oxygen to produce energy.

4) Combined exercise

An exercise that performs both aerobic exercise and resistance exercise simultaneously.

5) Obesity-related cardiovascular disease risk factors

All factors that negatively affect the heart or blood vessels, and are likely to develop into brain, heart, kidney, and artery damage, potentially leading to health problems or even death. The main factors include blood pressure, cholesterol, diabetes, obesity, and genetic factors.

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6) Muscle function

The function of a muscle, including muscle strength, muscular endurance, and muscle power exerted by a contracting muscle.

7) Skeletal muscle metabolism

Skeletal muscle metabolism is all chemical reactions, including the transport of substances between cells within skeletal muscles, and skeletal muscle metabolism includes immune cells and muscle cells and is regulated by various signaling pathways activated or suppressed by nutrition, hormones, inflammation and nerve stimulation.

8) Muscle hypertrophy

The enlargement of skeletal muscles through an increase in muscle size, leading to a certain increase in muscle strength.

9) Mitochondrial biogenesis

An increase in the number and size of mitochondria, and mitochondrial biogenesis in skeletal muscle occurs mainly through the stimulation through aerobic exercise.

10) Mechanistic target of rapamycin (mTOR)

A down-stream molecule of insulin-like growth factor 1 (IGF-1), a protein that induces cell growth and muscle synthesis, and plays an important role in muscle strength and hypertrophy.

11) AMP-activated protein kinase (AMPK)

An enzyme that acts as a sensor in maintaining intracellular energy homeostasis and is closely related to the regulation of energy metabolism through fatty acid oxidation and glycolysis.

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12) Peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC1-α)

A transcription factor associated with the regulation of mitochondrial function and cellular energy metabolism and is closely related to the maintenance or increase of mitochondrial biogenesis in skeletal muscle.

13) Fibronectin type III domain-containing protein 5 (FNDC5)

A hormone derived from skeletal muscle that changes white fat into brown fat and induces heat production to increase body energy consumption. It is known as a potential therapeutic agent for obesity and related diseases.

14) Insulin like growth factor 1 (IGF-1)

An anabolic hormone that increases the rate of muscle fiber protein synthesis and mediates satellite proliferation and differentiation.

15) Ca^{2+}/calmodulin-dependent protein kinase (CaMK)

An intracellular calcium ion and calmodulin-dependent protein enzyme that plays a role in mediating important actions such as inflammation, metabolic action, cell apoptosis, muscle contraction, short-term and long-term memory, and immune response.

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II. Literature review

1. Circadian rhythm and obesity

All the living beings on Earth live in accordance with the 24-hour cycle caused by the rotation of the Earth. The circadian rhythm influences the sleep-wake cycle, body temperature changes, neurotransmission and hormonal signals, heart rate, and metabolic processes (Golombek & Rosenstein, 2010). The cells in all mammals, including humans, share molecular mechanisms, including the circadian rhythm. The circadian clocks can be divided into the central clock and peripheral clocks, which are located in the muscles, heart, liver, kidneys, adrenal glands, and so on (Albrecht, 2012; Allada & Bass, 2021). The central clock is present in the suprachiasmatic nucleus (SCN), and the peripheral organs have a peripheral clock. When light enters the retina, the electrical signals generated pass through the hypothalamus, and this connection is used by the central clock to activate the relevant hormones and motor nerves. In order to maintain a smooth circadian rhythm, a light-dark cycle of 24 hours is essential. Mice with different light-dark cycles showed problems with arrhythmia and feeding cycles, and unfavorable physical changes due to errant circadian rhythms, demonstrating that light is an important factor in regulating the circadian rhythm (Chiesa et al., 2010; Tahara et al., 2012). The central clock is controlled by light, whereas the peripheral clocks may be activated by temperature, exercise, diet, and various external factors. Previous studies that confirmed the association between the peripheral clock and circadian rhythm; if the breakfast, lunch, and dinner times was delayed by 5 hours, the expression of the clock gene was also similarly delayed (Shibata et al., 2010; Wehrens et al., 2017). Previous studies clearly explained the relationship between the circadian rhythm and obesity in accordance with the biological clock and mealtime.

Obesity is a condition in which the level of fat accumulation in the body causes health problems. Obesity occurs for a variety of reasons, including lifestyle habits, mealtimes, and work shifts. In particular, the incidence of obesity is highest among

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shift workers, which explains that the change in sleep-wake cycle according to the circadian rhythm could cause obesity (Orihara et al., 2020; Zhu et al., 2019).

Previous studies have reported that people with obesity retire to bed later, and sleep time and quality are also lower than that in healthy people. Obesity suggested a direct association with disturbances in circadian rhythms and problems in the metabolic process. McHill et al. (2017) reported that melatonin, a hormone that facilitates the onset of sleep, was highly correlated with the amount of calories consumed 4 hours before the beginning of sleep, and that the circadian rhythm, obesity, and sleep were also closely related. Researchers reported that the increase in the population of people with obesity was a global public health problem, leading to economic and social burdens, and required continuous management (Karlsson et al., 2001; Shan et al., 2018). Although a review of previous studies on obesity and circadian rhythm did not provide clear evidence, lifestyle-related sleep disturbances have been shown to increase body weight and body fat and alter energy metabolism. Imbalances in sleep/wake cycles alter the circadian clock, indicating a close relationship between obesity and circadian rhythm (Bray & Young, 2007; Visscher & Seidell, 2001; Vorona et al., 2005). This interrelationship is being introduced as a novel solution to control obesity and is different from calorie intake and energy consumption, which is currently used to manage obesity (Colles et al., 2007). In particular, many recent studies provided observations on the timing of food intake. It was reported that the errant regulation of the clock gene increases the risk of developing metabolic syndrome in rats, and that a high-fat diet was directly associated with the circadian behavior and pattern of metabolic gene expression (Kohsaka et al., 2007; Turek et al., 2005). The weight gain in those who did not take breakfast and ate late at night could be determined by the timing of food intake. Accordingly, O’reardon et al. (2004) raised the need for a thorough study to confirm the relationship between the circadian rhythm and obesity. Sleep habits and work patterns that disrupt the circadian rhythm, and the habits and timing of food intake are closely related to human metabolism and sleep disorders, and furthermore,

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can increase the risk of obesity. Accordingly, regulating the biological clock is an important therapeutic method for managing obesity.

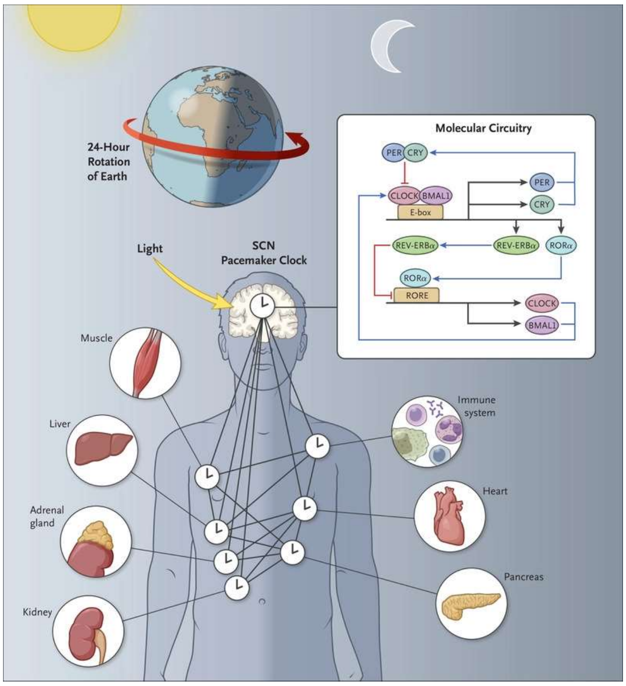

Figure 1. Circadian networks (Allada & Bass, 2021)

2. Exercise and circadian rhythm

For the general population and athletes, exercise is mainly performed based on endurance or resistance training to increase physical strength and maintain health. Endurance exercise is a type of aerobic exercise that uses oxygen to generate adenosine triphosphate (ATP) for energy metabolism. Improvement of endurance primarily involves improving mitochondrial biogenesis and function. Training for endurance improvement should be carried out over several months or years so that the effects are evident. AMPK is a molecular biological marker related to improved endurance and plays a central role in skeletal muscle metabolism (Lantier et al., 2014). A study by Hardie et al. (2012) confirmed the association between

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mitochondrial function and muscle contractility by knocking out AMPK in mice. The mice without functional AMPK showed reduced exercise capacity; additionally, the lack of AMPK decreased mitochondrial respiration, proving that AMPK is a marker that regulates muscle metabolism.

Resistance exercise is a form of exercise performed to increase muscle strength and muscle mass and induces muscle hypertrophy through the growth and proliferation of myofibers (Qaisar et al., 2016). Among the muscle fiber types, resistance exercise causes the preferential hypertrophy of type II muscle, because it responds to stimuli such as muscle contraction with a faster plasticity compared to type I muscle fibers (Aagaard et al., 2001; Mero et al., 2013; Phillips, 2009). Resistance exercise for 6 to 10 weeks resulted in the hypertrophy of type II muscle; therefore, the plasticity of type II muscle to resistance exercise was confirmed. In addition, a study reported that long-term resistance exercise increased the cross-sectional area and strength of type II muscle fiber when compared to type I muscle fiber (Smith & Merry, 2012). In addition, the number of satellite cells in type II fibers was considered to be a response to resistance training. Although the number of satellite cells was previously distributed in type I muscles, the number of satellite cells in type II muscles after resistance exercise was higher than that in type I muscles, indicating resistance. Type II muscle hypertrophy for training was explained in more detail (Crameri et al., 2004). Resistance exercise produces the most effective hypertrophy when performed at an intensity of 60% or more of 1RM (1 Repetition maximum) and increases mTOR. mTOR was increased through resistance exercise, in addition to PI3K and Akt; therefore, the mTOR signaling pathway explained the mechanism of muscle hypertrophy (Bodine, 2006; Kumar et al., 2009).

Muscle hypertrophy responds primarily to the circadian rhythm regulated by light, and stimulating skeletal muscle cells through exercise expresses molecular clock genes and shows a clear relationship between circadian rhythm and muscle hypertrophy and metabolic function (Bodine et al., 2001; Koopman et al., 2006). Changes in the

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muscle protein synthesis in mice were used to study the circadian rhythm-related changes at the molecular level in skeletal muscle (Reeds et al., 1986). McCarthy et al. (2007) and Miller et al. (2007) confirmed the existence of 215 genes in mice and 107 genes in the skeletal muscle of mice and reported correlations with circadian rhythm and exercise.

Brain and Muscle ARNT-Like 1 (BMAL1) is a major marker for circadian rhythm, and the circadian clock is mainly dependent on BMAL1 and Circadian Locomotor Output Cycles Kaput (CLOCK) (Ray et al., 2020). Muscle contraction and growth through exercise were shown to be involved in the expression of MyoD1, Myogenin, and Calmodulin 2. BMAL1 also regulated the expression of the metabolic markers pyruvate dehydrogenase kinase 4 (PDK4), peroxisome proliferator-activated receptor-gamma coactivator-1 beta (PGC1-β), and uncoupling protein 3 (UCP3) (Camera, 2018).

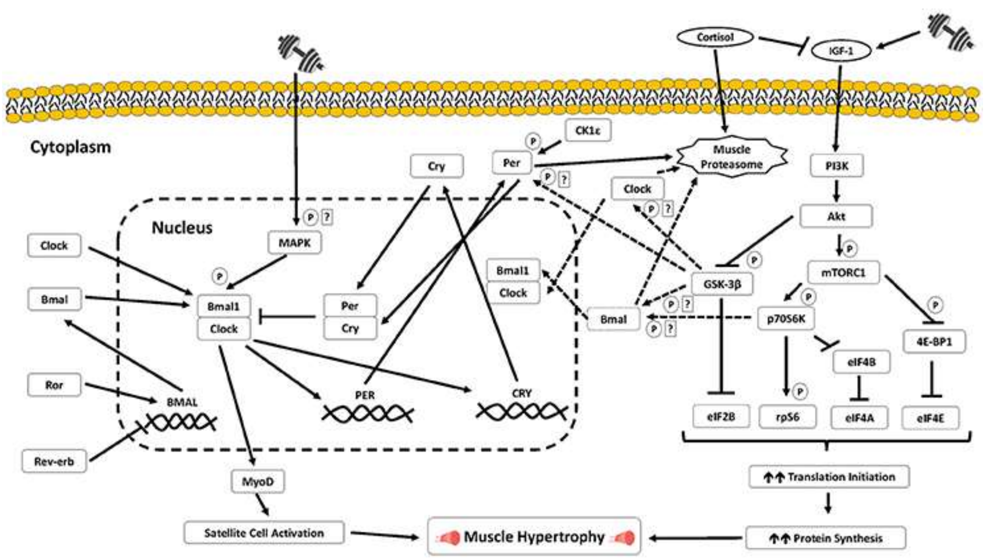

Figure 2. Circadian regulation of muscle growth (Camera, 2018)

In mice with BMAL1 knockout, the expression of actin, myosin, and titin were decreased, the structure of musculoskeletal muscle fibers was deteriorated, and mitochondrial dysfunction was observed. The relationship between circadian rhythm

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and skeletal muscle metabolism was clearly explained (Andrews et al., 2010; Dyar et al., 2014). In particular, it has been reported that Rev-erbα deficiency in the skeletal muscle reduces exercise capacity due to decreased mitochondrial generation (Woldt et al., 2013). So far, changes in exercise and circadian rhythm at the physiological and molecular level have been confirmed. Previous studies conducted on humans partially agree with the results obtained from experimental animals.

Observing the results of exercise performed at 8 AM and 6 PM, it was reported that blood glucose and respiratory exchange rate were more positive in the morning than in the evening. Additionally, a study by Ezagouri et al. (2019) reported that morning exercise reduces blood sugar levels and uses fat as the main energy source with low RER. These research results can help manage obesity. In addition, the results of the anaerobic power performance test conducted on elite athletes showed higher pedaling power at 6 PM than at 8 AM and 1 PM. Circadian rhythms influenced changes in motor performance (Deschodt et al., 2004). The relationship between exercise and circadian rhythm has been continuously studied on experimental animals and humans, and exercising in accordance with the circadian rhythm directly or indirectly explains the relationship between muscle hypertrophy and mitochondrial biogenesis.

3. Combined exercise and exercise order

It is evident from the results of multiple studies that endurance and resistance exercises have different physical effects. Firstly, endurance exercise induced favorable changes to aerobic and metabolic functions through improved mitochondrial biogenesis and function in skeletal muscle. Resistance exercise acted as a preventive measure against sarcopenia; due to continuous muscle contraction, muscle hypertrophy was induced through the expression of mTOR, a protein synthesis biomarker. The results that have been obtained from animal experiments are limited in their application to humans. A previous study reported that aerobic exercise performed by humans

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decreased the risk factors for cardiovascular disease, whereas resistance exercise increased the risks (Okamoto et al., 2006; Sugawara et al., 2006). Additionally, some studies showed that combined exercise did not induce a favorable change in the risk factors for cardiovascular disease. Conversely, some studies suggested that the efficacy of combined exercise in humans was controversial (Cook et al., 2006; Kawano et al., 2012). Combined exercise is being used as a therapeutic method to reduce weight and increase muscle mass in participants with obesity. Combined exercise favorably changed the physical strength and cholesterol compared to endurance exercise (Lambers et al., 2008). Additionally, endurance and resistance exercises are mainly used as therapeutic methods to prevent age-related sarcopenia (Lee et al., 2019; Zamboni et al., 2019). It is self-evident that it does not induce hypertrophy to the same levels as resistance exercise. Therefore, it is necessary to apply a combination of aerobic and resistance exercise (Nasiri et al., 2018; 2015; Phu et al., 2015). However, despite the potential benefits of this combination, it has been reported through many studies that it has negative effects (Hickson, 1980; Wilson et al., 2012). Therefore, evidence is scarce on which exercise must be performed first in a combined exercise regimen, to maximize the benefits.

The signaling network between resistance exercise and endurance exercise has been almost clearly elucidated through many studies (Atherton et al., 2005; Coffey & Hawley, 2007). The effect of sustained resistance exercise induces muscle fiber hypertrophy for up to 48 hours (Fry, 2004). Some studies generally do not recommend aerobic exercise after resistance training because it could induce muscle weakness or hypertrophy (Bell et al., 2000). The offsetting of the effects of endurance exercise and resistance exercise is called the interference effect. The interference effect is primarily explained through molecular biological signaling pathways using experimental animals. Aerobic exercise phosphorylates AMPK and facilitates the translocation of proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) to the nucleus. Resistance exercise is associated with IGF-1 and Akt. It improved muscle size and strength owing to protein synthesis through the mTOR

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signaling pathway. Representative AMPK expressed through aerobic exercise caused an interference effect that blocked the induction of hypertrophy through a signaling pathway that phosphorylated TSC complex subunit 2(TSC2) and inhibited mTOR, a marker of hypertrophy, when aerobic exercise was performed after resistance exercise (Hawley, 2009). For this reason, researchers recommend that resistance exercise when performed after aerobic exercise negatively affects the protein synthesis pathway; therefore, in order to attain muscle hypertrophy, resistance exercise must be performed after aerobic exercise (Fyfe et al., 2014). Interestingly, however, the results from human studies varied from those performed on experimental animals. Aerobic exercise, when performed before resistance exercise, showed a greater increase in muscle mass compared to the group that continued to perform only resistance exercise, which explains why aerobic exercise may not suppress hypertrophy, which is an effect of resistance exercise (Lundberg et al., 2013). In addition, the meta-analysis study conducted by Wilson et al. (2012) to confirm the interference effect of exercise also proved that there was an interference; however, Murach & Bagley (2016) did not observe the interference effect of the exercise order. Therefore, continuous research is required to provide a clear rationale for the exercise order during combined exercise.

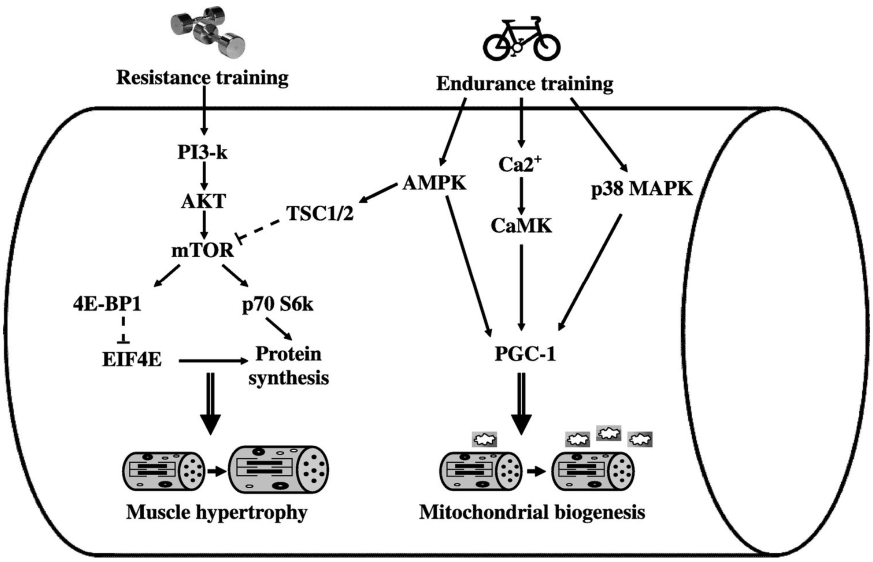

Figure 3. Molecular responses to exercise orders (Fyfe et al., 2014)

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III. Study Ⅰ: Effect of combined exercise according to circadian rhythm and exercise order on body composition, physical fitness, obesity-related cardiovascular disease risk factors, upper and lower extremity muscle functions, and sleep quality in adult women with obesity.

1. Research significance

The rapid development of science and technology has brought convenience and abundance to people, while simultaneously causing excessive nutritional intake and a decrease in the amount of physical activity. In addition, the COVID-19 pandemic, which began in 2019, led to a decrease in physical activity by paralyzing the global economic market, economic contraction, and the adoption of the work-from-home format. Decrease in physical activity is known to increase body fat, reduce skeletal muscle mass, and cause obesity. Obesity is a serious social problem that increases the incidence of lifestyle diseases such as diabetes, high blood pressure, dyslipidemia, and hyperinsulinemia (Consitt et al., 2009). Recently, the association between the circadian rhythm and obesity has been reported as a suitable practice to more effectively prevent and manage obesity (Broussard & Van Cauter, 2016; Li et al., 2020). Circadian rhythm refers to the periodic environmental changes that occur over a cycle of about 24 hours. The circadian rhythm is regulated by the suprachiasmatic nucleus in the hypothalamus of the brain and is stimulated by external environmental factors. This rhythm is closely related to various physiological changes such as heart rate, stress, metabolism, sleep quality, immunity, and hormone secretion (Panda, 2016; Peek et al., 2017). The circadian rhythm and exercise are closely related to sleep,

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and a study by Bonardi et al. (2016) reported that both aerobic and resistance exercises improved sleep quality and highlighted the relationship between exercise and sleep. Exercise induced changes in the heart rate, hormones, and metabolic function to help manage obesity and insulin resistance and recover from muscle fatigue, and circadian rhythms during exercise must be considered (Ünver & Atan, 2021; Saner et al., 2018; Wolff & Esser, 2012). Kinesiology and health researchers recommended exercise therapy as the most economical and effective way to manage obesity. Aerobic and resistance exercises were mainly used to treat obesity, but the effects of the two exercises induced different physical changes (Villareal et al., 2017).

Aerobic exercise is being introduced as a method to reduce body fat, promote fatty acid oxidation in the body, and improves the cardiovascular system and cardiorespiratory endurance (Chapman et al., 2013). Resistant exercise is known to improve muscle mass and strength by increasing anabolic hormones such as testosterone and IGF-1, which represent protein synthesis (Mitchell et al., 2013). Therefore, aerobic and resistance exercise each promote different physical changes, and the idea of combined exercise is gaining attention because it can compensate for the shortcomings of one type of exercise. Combined exercise, which includes aerobic and resistance exercise, is very effective in reducing body fat, increasing muscle mass, improving blood lipids, and increasing anabolic hormones, and it has been reported through many studies that it induces positive physical changes compared to a single type of exercise (Wilson et al., 2012). Previous studies showed different changes in strength, anabolism, stress hormones, free fatty acids, and catecholamines depending on the aerobic exercise and resistance exercise order, and thus did not suggest an effective exercise order (Drummond et al., 2005; Kang & Ratamess, 2014; Rosa et al., 2015). In addition, there were few studies that presented the timing and order of exercise for effectively treating obesity by considering the circadian rhythm and exercise order. In this study, we aimed to confirm the effect of combined exercise with respect to the circadian rhythm and exercise order.

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2. Research purpose

The purpose of this study was to investigate the effects of 8 weeks of combined exercise with respect to the circadian rhythm and exercise order on body composition, physical fitness, obesity-related cardiovascular disease risk factors, upper and lower extremity muscle functions, and sleep quality in adult women with obesity.

3. Materials and methods

1) Research participants

G×Power 3.1 was used to determine the optimal sample size (Effect size=0.35, Power=0.97, Sample size=40) before recruiting participants for this study (Faul et al., 2009). This study recruited women with obesity (n=55) who had a percentage body fat of 30% or more, and had not been diagnosed with cardiovascular and musculoskeletal diseases in the last 6 months. The following participants were excluded from this study: (% body fat < 30%, n=3), (severe morning and evening types, n=2). The 50 participants were randomly assigned into five groups, each of which represented a particular order and timing of the exercise: aerobic-resistance exercise in the morning (MARG, n=10), resistance-aerobic exercise in the morning (MRAG, n=10), aerobic-resistance exercise in the evening (EARG, n=10), resistance-aerobic exercise in the evening (ERAG, n=10), and obesity control group (OCG, n=10). Three participants of MARG (n=2) and MRAG (n=1) withdrew from the study due to personal circumstances, and participants of EARG (n=2) and ERAG (n=1) whose exercise participation rate was less than 80% were excluded from the analysis. The study participants provided written consent, and the study design was

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approved by the Jeju National University Institutional Review Board (JJNU-IRB-2021-045-001).

The characteristics of the study participants are provided in <Table 1>.

Table 1. Characteristics of participants

Variables \ Group	OCG (n=10)	MARG (n=8)	MRAG (n=9)	EARG (n=8)	ERAG (n=9)
Age (yrs)	24.00±3.43	22.5±3.51	22.00±2.06	24.75±3.77	23.55±4.29
Height (cm)	163.03±5.80	161.68±5.00	162.06±3.38	157.83±5.74	162.60±4.32
Weight (kg)	68.55±17.41	65.07±12.39	68.31±8.13	66.61±14.62	65.85±9.79
%Fat (%)	38.35±5.70	35.37±4.21	35.82±5.17	37.27±4.02	35.67±5.40
BMI (kg/m^2)	25.65±5.88	24.73±3.50	26.01±3.01	26.60±5.11	24.90±3.52
MEQ (score)	45.33±7.30	44.87±7.95	44.75±11.09	41.15±10.02	46.22±8.19

Mean±standard deviation

BMI, body mass index; %Fat, percent body fat; MEQ, morningness-eveningness questionnaire; OCG, obesity control group; MARG. aerobic-resistance exercise in the morning group; MRAG, resistance-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group

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2) Study design

The study design of this study was to determine the effect of an 8-week exercise program according to the circadian rhythm and exercise order on the body composition, obesity-related cardiovascular disease risk factors, upper and lower extremity muscle functions, and sleep quality in obese adult women. The overall experimental design of this study is shown in <Figure 4>.

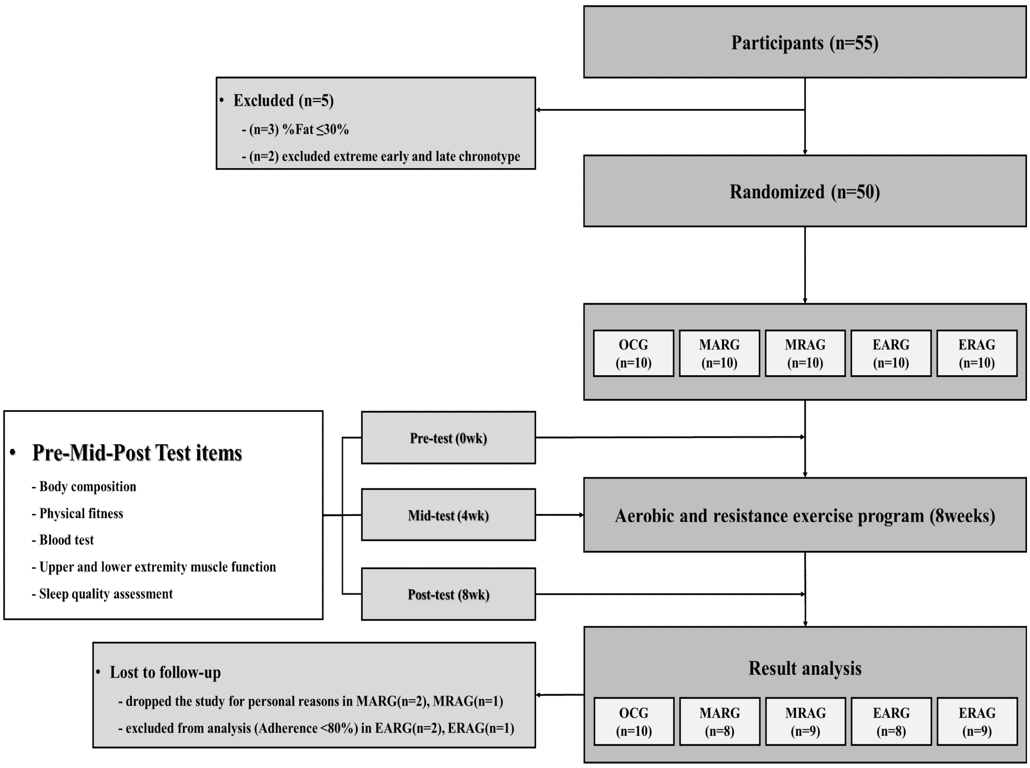

Figure 4. The study design for study Ⅰ

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3) Combined exercise program

This study utilized a combined exercise program that was to be performed thrice a week for 8 weeks. Each group performed a different order of aerobic and resistance exercise in either the morning or evening. All participants performed adaptive exercise for one week, following which the maximum heart rate and 1RM were measured to set the exercise intensity for participants before starting the exercise program. The aerobic exercise intensity was set using the Karvonen formula (206.9 - (0.67 × age)), and treadmill exercise was performed for 30 minutes at the most effective 60 – 70% maximum heart rate (HRmax) intensity for fat burning (Gellish et al., 2007).

The resistance exercise intensity was set up using the 1RM indirect estimation formula [1RM = wt + (wt × 0.025 × reps)] for each exercise item, and the exercise intensity was increased by applying the principle of overload at 0 – 4 weeks (60-80% 1RM) and 5 – 8 weeks (70-80% 1RM). Resistance exercise consisted of exercises involving push-and-pull and weight bearing, and was performed for 1 second of concentric and 2 seconds of eccentric contraction. Three sets of 10 repetitions were performed, with 2 minutes of rest in between sets. Resistance exercise was performed using weight training machines to minimize possible injuries to the study participants, and dynamic stretching and exercises using form rollers were performed for 5 minutes each during warm-up and cool-down for inducing the best condition and rapid muscle fatigue recovery. The combined exercise program of this study is shown in <Table 2>.

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Table 2. Combined exercise program

	Contents of exercise			Reps	Set/Rest (min)	Time (min)	Frequency (day/weeks)	Period and Intensity
Warm-up	Dynamic Stretching					5		
Aerobic exercise	Treadmill exercise			1	1	30	3/8	60-70% HRmax
Resistance exercise	**Day 1 (Push)**	**Day 2 (Pull)**	**Day 3 (WB)**	10	3/2	30	3/8	0-4 weeks: 60-80% 1RM 5-8 weeks: 70-80% 1RM
	Chest press	Seated row	Modified push-up					
	Shoulder press	Let pull down	Back extension					
	Leg extension	Leg curl	Squat					
	Triceps extension	Biceps curl	Lunge					
	Crunch	Leg raise	Sit-up					
Cool-down	Foam roller exercise					5		

WB, Weight bearing; 1RM, One repetition maximum

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4) Measurements

(1) Physique and body composition

Physique and body composition were measured using machines such as the Height, Weight Scale (DS-103M, Dong San Jenix, Seoul, Korea) and body composition analyzer (Inbody 770, Inbody, Seoul, Korea). The participants visited the laboratory for their pre-prandial analyses at 9 a.m. thrice over the course of the study (before the study, and 4 and 8 weeks after study commencement) for 8 hours.

(2) Physical fitness

Physical fitness was measured using the measurement items and tools shown in <Table 3> before, and 4 and 8 weeks after, combined exercise.

Table 3. Materials and device for physical fitness measurement

Physical fitness	Physical fitness Items	Measuring Instruments	Apparatus
Muscular strength	Grip strength (kg)	Digital dynamometer	T.K.K.-5101, TAKEI, Japan
	Back strength (kg)	Digital back-dynamometer	T.K.K.-5402, TAKEI, Japan
Muscular endurance	Sit-up (reps/60sec)	Sit-up board	T.K.K.-5505, TAKEI, Japan
Flexibility	Sit and reach (cm)	Trunk extension backward measurement	T.K.K.-5412, TAKEI, Japan
Cardiorespiratory endurance	Harvard step test	Step box (45cm)	Step box, Iwanna, China
		Electronic metronome	SMT-1000, SAMICK, Korea

reps, repetitions

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① Muscular strength

Muscular strength (grip and back strength) were measured at previous, 4 weeks, 8 weeks after combined exercise.

- Grip strength was measured using a digital dynamometer (T.K.K. 5101, TAKEI, Japan) with the feet at shoulder-width distance. The width of the dynamometer was adjusted such that the second joint of the finger was at a right angle to it. Measurements were made by applying the maximum strength and pulling the handle for 2 to 3 seconds while the distance between the body and the arm was straightened at about 15°. It was measured twice, and the maximum value of the dominant hand was recorded in units of 0.1 kg.

- Back strength was measured using a back strength dynamometer (T.K.K. 5402, TAKEI, Japan). The participants were asked to stand with their feet 15cm apart on the foot of the back strength meter, and bend their upper body by about 30˚ and hold the handle of the back strength meter. The participants raised the upper body and applied the maximum force for 3 seconds to pull the handle. Measurement was performed twice, and the maximum value was recorded in units of 0.1 kg.

② Muscular endurance

Muscular endurance (Sit-up) was measured before, and 4 and 8 weeks after, combined exercise.

To measure muscular endurance, the participants laid down on a sit-up device (T.K.K. 5505, TAKEI, Japan) and bent their knees about 90°. At the start signal, they would bend their body forward, let both elbows touch both knees, and then lie down again for 60 seconds. The maximum number of times that a participant could

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perform this exercise was recorded.

③ Flexibility

Flexibility (Sit and reach) were measured before and after 4 and 8 weeks of combined exercise.

Flexibility test was performed using a sit and reach device (T.K.K. 5111, Takei, Japan). The participant had to sit on the board with the distance between their feet not exceeding 5 cm. After measuring twice by holding the posture for 3 seconds, the maximum distance was recorded in cm.

④ Cardiorespiratory endurance

Cardiorespiratory endurance (Havard step test) was measured before, and 4 and 8 weeks after, combined exercise.

The physical efficiency index (PEI) was calculated through the Harvard step test. The Harvard step test was performed using a metronome (120bpm) for 3 minutes to climb and land exercise on the 45 cm height box (Iwanna, China). The heart rates were measured between 1 minute to 1 min 30 seconds, and 2 minutes to 2 minutes 30 seconds, and 3 minute to 3 minutes 30 seconds. The PEI calculation by using long form equation - fitness index formula was as follows. <Long Form Equation - Fitness Index = (100 x test duration in seconds) divided by (2 x sum of heart beats in the recovery periods)>

(3) Upper and lower extremity muscle function

Upper and lower extremity muscle function were measured at previous, 4 weeks, 8

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weeks after combined exercise.

① Upper extremity muscle function

- Abdominal power test

The abdominal power test was performed according to the method reported in Cowley & Swensen. (2008). This test consisted of the front and side abdominal power test (FAPT and SAPT).

FAPT was performed as follows: the participant laid down while holding the medicine ball (2% body weight) with the knee bent 90° and both arms spread on the mat. FAPT was measured twice by contracting the abdominal muscles and raising the upper body to throw the medicine ball forward from the knee line <Figure 5>.

SAPT was performed as follows: the participant sat on the mat (knee angle 90°, hip angle 45°), held the medicine ball (2% body weight), and the measurements were taken twice by turning the upper body 90° outward to the opposite direction and then inward again to throw the medicine ball from the knee line <Figure 6, 7>. FAPT and SAPT presented the maximum distance by measuring from the toe of the participant to the point where the ball fell.

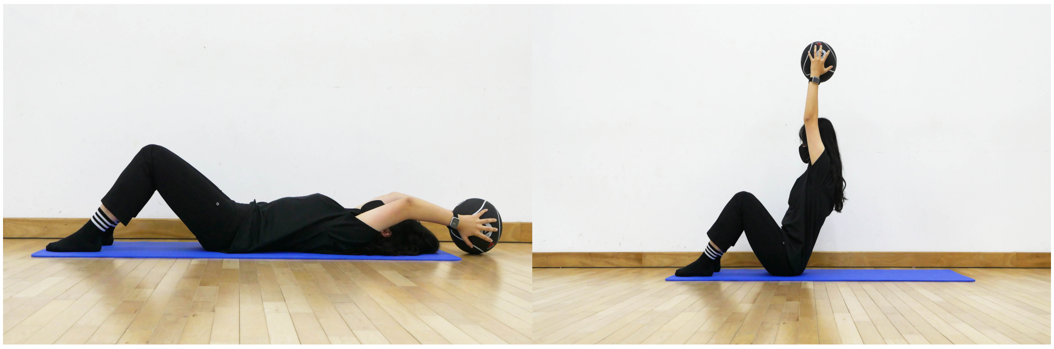

Figure 5. Front abdominal power test

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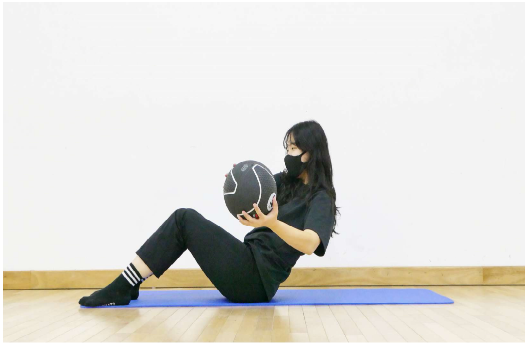

Figure 6. Left side abdominal power test

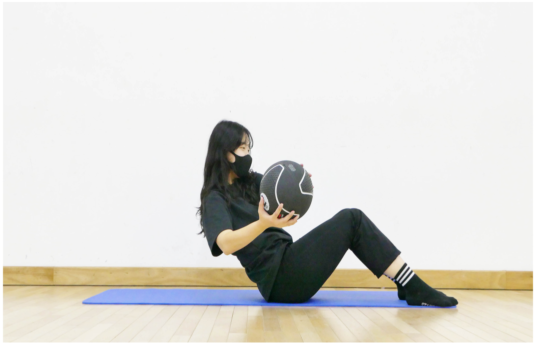

Figure 7. Right side abdominal power test

• Trunk flexor endurance test

The trunk flexor endurance test (TFET) was performed to evaluate the endurance of abdominal muscles. According to the method described by Arman et al. (2021), the ankle was fixed to the floor, with the hip and knee angle at 90°, and the arms crossed in front of the chest. Thereafter, the time (in seconds) for removing the support and maintaining the angle of the waist at 60° was recorded <Figure 8>.

Figure 8. Trunk flexor endurance test

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② Lower extremity muscle function

Lower extremity muscle function was measured before, and 4 and 8 weeks after, combined exercise.

- Vertical jump test

Vertical jump tests were performed twice using a digital vertical jump device (DW771A, SKARO, Korea) and the maximum height (cm) was measured. Fatigue was minimized by taking a break for about 2 minutes after one measurement

- Sit-to-stand test

This test, which was described by Martinez-Hernandez & Dehghani-Sanij. (2019), evaluated the lower extremity muscle function. For the measurement, the participants sat on a 43 cm-high chair, crossed their arms at chest level, put their palms on their shoulders, and sat down and stood up for 30 seconds until their knees were completely straightened. The number of repetitions performed in 30 seconds was recorded.

(4) Obesity-related cardiovascular disease risk factors

Obesity-related cardiovascular disease risk factors consisted of fasting blood sugar and blood lipids. This test was performed pre-prandially in the morning before, and 4 and 8 weeks after, combined exercise.

① Fasting glucose

Fasting glucose was analyzed using a disposable blood collection needle

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(Acu-Chek®Softclix, Roche, Mannheim, Germany) and blood glucose meter (Acu-Chek®Guide, Roche, Mannheim, Germany).

② Blood lipid

The total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured using Mission Cholesterol Meter (Acon Laboratories, Inc. San Diego, CA, USA).

(5) Morningness-eveningness questionnaire

The identification of circadian rhythm types was developed by Horne & Östberg (1976), and Lee et al. (2014) used the Korean translation of MEQ-K. Cronbach's α coefficient for the item internal consistency of MEQ-K was 0.77, and reliability and validity were verified with a sample fit of 0.847. The MEQ consisted of 19 questions, and a score of 0 to 6 points was assigned to each question. According to the score received, the results were divided into 5 categories.

(6) Pittsburgh sleep quality index

Sleep quality was evaluated using the Pittsburgh sleep quality index (PSQI) before, and 4 and 8 weeks after, combined exercise. The PSQI is a tool that subjectively evaluates the quality of sleep, such as the amount, depth, and comfort of sleep. This study used the Korean version of the Pittsburgh Sleep Quality Index (K-PSQI) (Sohn et al., 2012). K-PSQI showed high reliability for internal consistency (Cronbach's α 0.84). The PSQI is divided into 7 sub-domains (subjective sleep quality, sleep latency, sleep time, usual sleep efficiency, sleep disturbance, use of sleeping pills, and dysfunction during the day), each with a score of 0 to 3. Therefore, the higher the average score over the 7 domains, the poorer the quality of sleep.

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(7) Statistical analysis

The mean and standard deviation of all variables were calculated using the SPSS for windows (Version 21.0) statistical program. The detailed statistical processing method that confirmed the difference between the period and groups is as follows.

① Two-way repeated measures ANOVA was performed to verify the effect of interaction between groups and periods of all variables.

② To compare the differences between groups, one-way ANOVA was performed, followed by the Scheffe post-hoc test.

③ The significance level was set at $p<0.05$.

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4. Results

1) Body composition

(1) Body weight

<Table 4>, <Table 5> and <Figure 9> show the results of body weight changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 4> shows the descriptive statistics of body weight and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 5> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and the time period. There was significant difference in the interaction effect between group and period ($F=3.694$, $p=.003$) and between periods ($F=12.312$, $p=.001$), however, no significant difference was noted between groups ($F=.113$, $p=.977$).

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Table 4. The result of descriptive statistics and one-way ANOVA for body weight by measurement trial (kg)

Group	0wk	4wk	8wk	Total
OCG[1]	68.55±17.41	68.20±17.75	68.34±17.87	68.36±17.06
MARG[2]	65.07±12.39	64.30±12.32	64.11±12.02	64.49±11.71
MRAG[3]	68.31±8.13	66.81±8.38	64.81±7.64	66.64±7.88
EARG[4]	66.61±14.62	66.83±15.17	66.41±15.22	66.62±14.34
ERAG[5]	65.85±9.79	65.31±10.36	64.94±9.85	65.37±9.62
Total	66.96±12.46	66.36±12.77	65.80±12.63	66.37±12.62
F	.122	.114	.153	
p	.974	.977	.961	

Mean±standard deviation

OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

Table 5. The result of two-way repeated measures ANOVA for body weight

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	234.426	4	58.606	.113	.977	.011	.071
Error	20193.605	39	517.785				
Within Subject							
Period	29.252	1.557	18.786	12.312	.001	.040	.990
Group×Period	35.108	6.228	5.637	3.694	.003	.275	.946
Error	92.659	60.727	1.526				

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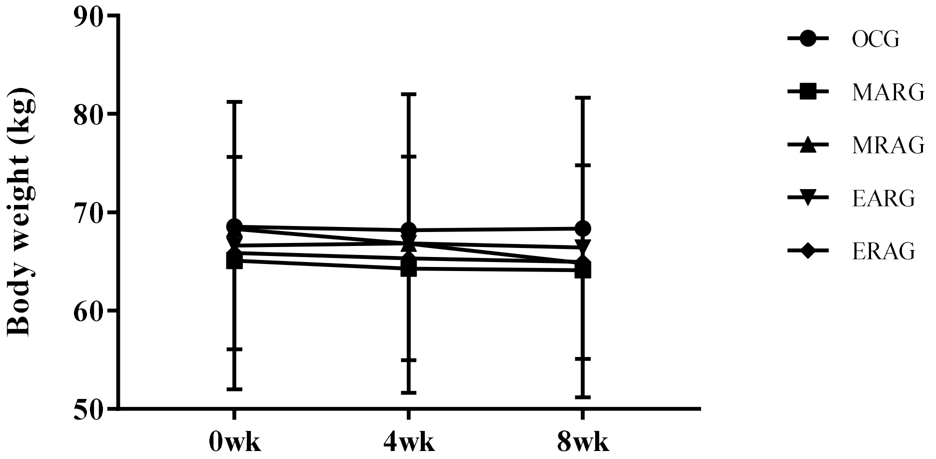

Figure 9. Change of body weight after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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② Body fat mass

<Table 6>, <Table 7> and <Figure 10> show the results of body fat mass changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 6> shows the descriptive statistics of body fat mass and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 7> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and the time period. There was significant difference in the interaction effect between group and period (F=2.553 p=.035) and periods (F=11.714, p=.001), however, no significant difference was noted between groups (F=.410, p=.800).

Table 6. The result of descriptive statistics and one-way ANOVA for body fat mass by measurement trial (kg)

Group	0wk	4wk	8wk	Total
OCG[1]	27.25±11.37	27.13±11.58	27.04±11.72	27.14±11.15
MARG[2]	23.22±6.70	22.65±6.79	22.53±6.12	22.80±6.26
MRAG[3]	25.55±5.49	24.50±5.68	23.06.±5.69	24.37±5.50
EARG[4]	25.16±7.79	25.20±8.02	24.76±83.10	25.04±7.62
ERAG[5]	23.70±6.27	23.72±6.15	22.90±6.12	23.44±5.95
Total	25.06±7.70	24.73±7.84	24.14±7.85	24.64±7.79
F	.373	.398	.511	
p	.827	.809	.728	

Mean±standard deviation

OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 7. The result of two-way repeated measures ANOVA for body fat mass

Variable	SS	df	MS	F	p	η^2	β
Between Subject							
Group	313.570	4	78.392	.410	.800	.040	.135
Error	7461.323	39	191.316				
Within Subject							
Period	18.766	1.342	13.982	11.714	.001	.231	.963
Group×Period	16.363	5.368	3.048	2.553	.035	.208	.769
Error	62.480	52.342	1.194				

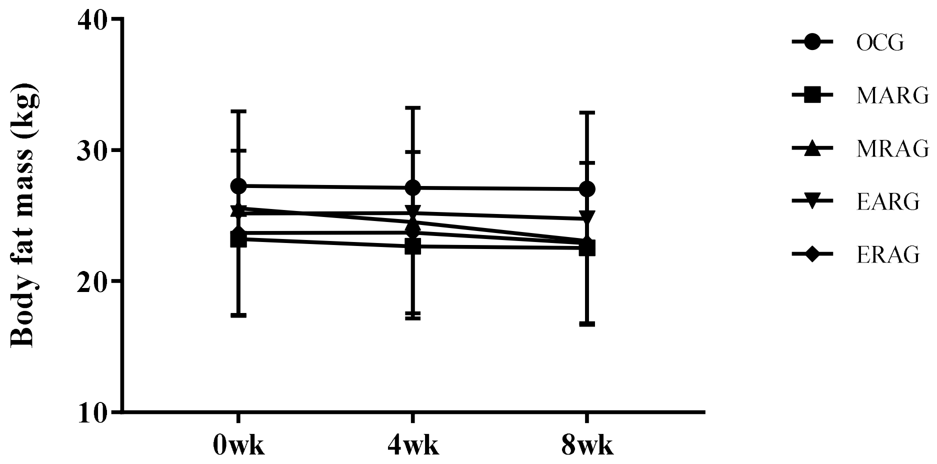

Figure 10. Change of body fat mass after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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③ Percent body fat

<Table 8>, <Table 9> and <Figure 11> show the results of percent body fat changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 8> shows the descriptive statistics of percent body fat and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 9> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and the time period. There was no significant difference in the interaction effect between group and period (F=.308 p=.926). And there was a no significant difference observed between groups (F=.751, p=.563) and periods (F=1.639, p=.208).

Table 8. The result of descriptive statistics and one-way ANOVA for percent body fat by measurement trial (%)

Group	0wk	4wk	8wk	Total
OCG[1]	38.35±5.70	38.36±5.68	38.30±5.96	38.34±5.58
MARG[2]	35.37±4.21	34.82±4.35	34.80±3.95	35.00±4.00
MRAG[3]	35.82±5.17	36.28±4.32	35.15±4.38	35.75±4.48
EARG[4]	37.27±4.02	37.16±4.02	36.72±4.41	37.05±3.98
ERAG[5]	35.67±5.40	35.96±4.62	35.10±5.08	35.58±4.86
Total	36.55±4.91	36.58±4.62	36.07±4.84	36.40±5.45
F	.592	.721	.866	
p	.670	.583	.493	

Mean±standard deviation

OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 9. The result of two-way repeated measures ANOVA for percent body fat

Variable	SS	df	MS	F	p	η^2	β
Between Subject							
Group	199.904	4	49.976	.751	.563	.072	.220
Error	2594.038	39	66.514				
Within Subject							
Period	7.163	1.446	4.954	1.639	.208	.040	.284
Group×Period	5.387	5.783	.931	.308	.926	.031	.126
Error	170.484	56.389	3.023				

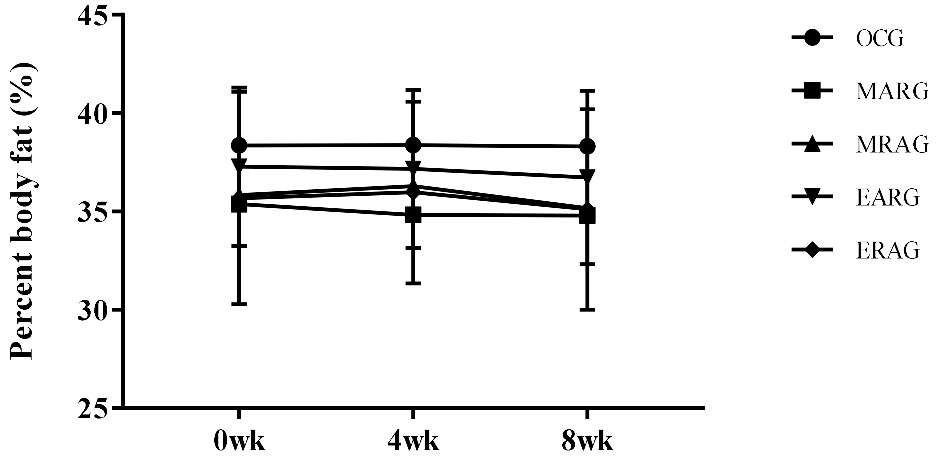

Figure 11. Change of percent body fat after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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④ Fat-free mass

<Table 10>, <Table 11> and <Figure 12> show the results of fat-free mass changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 10> shows the descriptive statistics of fat-free mass and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 11> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and the time period. There was no significant difference in the interaction effect between group and period (F=.907 p=.516). And there was a no significant difference observed between groups (F=.041, p=.997) and periods (F=1.224, p=.300).

Table 10. The result of descriptive statistics and one-way ANOVA for fat-free mass by measurement trial (kg)

Group	0wk	4wk	8wk	Total
OCG[1]	41.30±6.39	41.06±6.49	41.37±6.41	41.24±6.21
MARG[2]	41.85±6.76	41.65±6.44	41.57±6.86	41.69±6.39
MRAG[3]	42.76±3.08	42.31±4.06	41.86±2.77	42.31±3.24
EARG[4]	41.45±7.60	41.63±7.73	41.65±7.75	41.57±7.35
ERAG[5]	42.15±5.35	41.58±5.41	42.03±5.19	41.92±5.11
Total	41.90±5.72	41.63±5.83	41.69±5.71	41.74±5.75
F	.592	.721	.866	
p	.670	.583	.493	

Mean±standard deviation

OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 11. The result of two-way repeated measures ANOVA for fat-free mass

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	17.718	4	4.429	.041	.997	.004	.057
Error	4204.825	39	107.816				
Within Subject							
Period	1.563	2	.781	1.224	.300	.030	.260
Group×Period	4.627	8	.578	.907	.516	.085	.392
Error	49.771	78	.638				

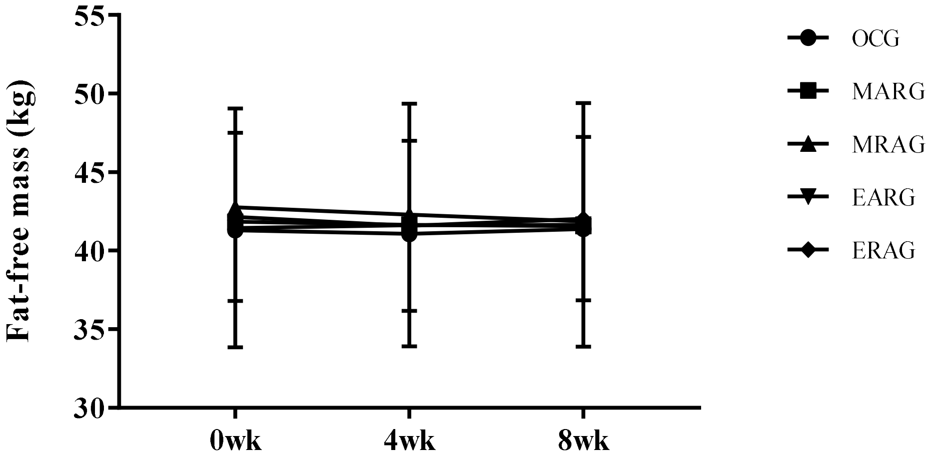

Figure 12. Change of fat-free mass after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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⑤ Body mass index

<Table 12>, <Table 13> and <Figure 13> show the results of body mass index changes in obese women after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 12> shows the descriptive statistics of body mass index and one-way ANOVA after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 13> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and the period. There was significant difference in the interaction effect between group and period (F=3.752, p=.003) and periods (F=13.277, p=.001); however, a no significant difference was noted between groups (F=.227, p=.891).

Table 12. The result of descriptive statistics and one-way ANOVA for body mass index by measurement trial (kg)

Group	0wk	4wk	8wk	Total
OCG[1]	25.65±5.88	25.54±5.99	25.56±6.03	25.58±5.76
MARG[2]	24.73±3.50	24.45±3.53	24.37±3.46	24.52±3.35
MRAG[3]	26.01±3.01	25.41±3.18	24.65±3.02	25.35±3.01
EARG[4]	26.06±5.11	26.67±5.32	26.48±5.29	26.58±5.01
ERAG[5]	24.90±3.52	24.71±3.67	24.54±3.43	24.71±3.40
Total	25.57±4.24	25.35±4.37	25.12±4.31	25.34±4.30
F	.258	.300	.332	
p	.903	.876	.855	

Mean±standard deviation

OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 13. The result of two-way measures repeated ANOVA for body mass index

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	65.736	4	16.434	.277	.891	.028	.105
Error	2314.02	39	59.334				
Within Subject							
Period	4.550	1.575	2.889	13.277	.001	.254	.989
Group×Period	5.144	6.301	.816	3.752	.003	.278	.951
Error	13.366	61.434	.218				

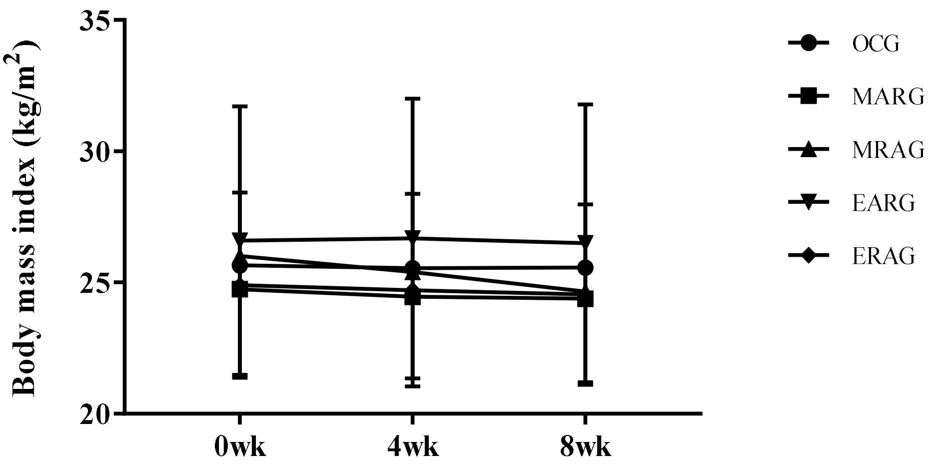

Figure 13. Change of body mass index after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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⑥ Waist circumference

<Table 14>, <Table 15> and <Figure 14> show the results of waist circumference changes in obese women after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 14> shows the descriptive statistics of waist circumference and one-way ANOVA after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 15> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and the period. There was no significant difference in the interaction effect between group and period (F=.494, p=.804) and between groups (F=.261, p=.901); however, a significant difference was noted between periods (F=12.912, p=.001)

Table 14. The result of descriptive statistics and one-way ANOVA for waist circumference by measurement trial (cm)

Group	0wk	4wk	8wk	Total
OCG[1]	83.10±13.71	83.77±10.72	80.80±15.03	82.55±12.88
MARG[2]	80.95±8.08	79.08±6.66	75.36±9.93	78.46±8.31
MRAG[3]	81.83±5.50	79.10±7.22	76.72±7.88	79.22±7.00
EARG[4]	85.20±13.75	83.52±12.70	77.37±16.92	82.03±14.34
ERAG[5]	82.03±8.78	80.48±9.46	77.46±11.70	79.99±9.85
Total	82.61±10.14	81.24±9.40	77.67±12.27	80.50±31.45
F	.194	.512	.231	
p	.940	.727	.919	

Mean±standard deviation
OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 15. The result of two-way repeated measures ANOVA for waist circumference

Variable	SS	df	MS	F	p	η^2	β
Between Subject							
Group	333.910	4	83.47	.261	.901	.026	.101
Error	12460.577	39	319.502				
Within Subject							
Period	599.326	1.443	415.287	12.912	.001	.249	.982
Group×Period	91.771	5.773	15.898	.494	.804	.048	.182
Error	1810.237	56.283	32.163				

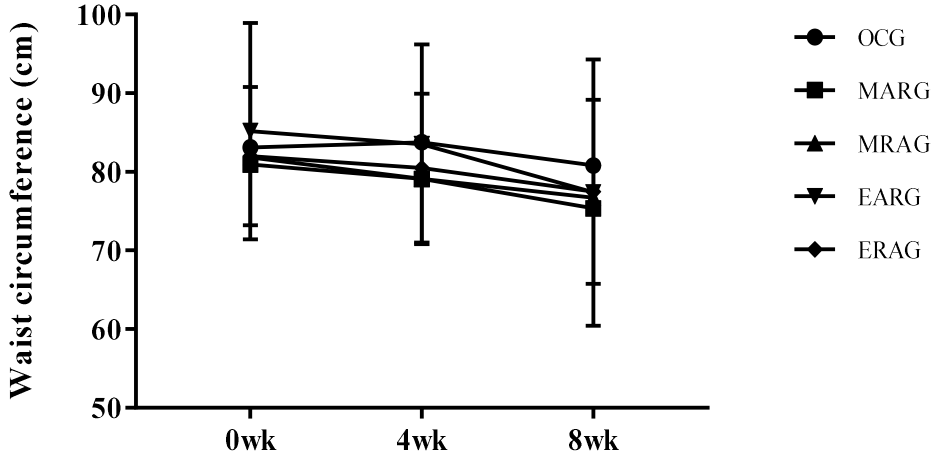

Figure 14. Change of waist circumference after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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⑦ Hip circumference

<Table 16>, <Table 17> and <Figure 15> show the results of hip circumference changes in obese women after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 16> shows the descriptive statistics of hip circumference and one-way ANOVA after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 17> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and the period. There was no significant difference in the interaction effect between group and period (F=.060, p=.999) and between groups (F=.216, p=.928); however, a significant difference was noted between periods (F=5.257, p=.013).

Table 16. The result of descriptive statistics and one-way ANOVA for hip circumference by measurement trial (cm)

Group	0wk	4wk	8wk	Total
OCG[1]	100.65±9.70	100.61±7.44	98.16±12.09	99.81±9.65
MARG[2]	98.23±8.36	97.52±7.87	94.65±10.38	96.80±8.69
MRAG[3]	99.62±7.16	98.50±10.54	95.18±11.11	97.77±9.57
EARG[4]	100.28±8.72	100.52±7.00	97.57±13.24	99.46±9.66
ERAG[5]	100.67±5.98	100.77±5.89	97.20±11.45	99.55±8.06
Total	99.94±7.77	99.63±7.65	96.61±11.22	98.72±8.88
F	.133	.298	.153	
p	.969	.877	.961	

Mean±standard deviation
OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 17. The result of two-way repeated measures ANOVA for hip circumference

Variable	SS	df	MS	F	p	η^2	β
Between Subject							
Group	179.944	4	44.986	.216	.928	.022	.091
Error	8139.523	39	208.706				
Within Subject							
Period	298.067	1.572	189.605	5.257	.013	.119	.747
Group×Period	13.556	6.288	2.156	.060	.999	.006	.063
Error	2211.154	61.310	36.065				

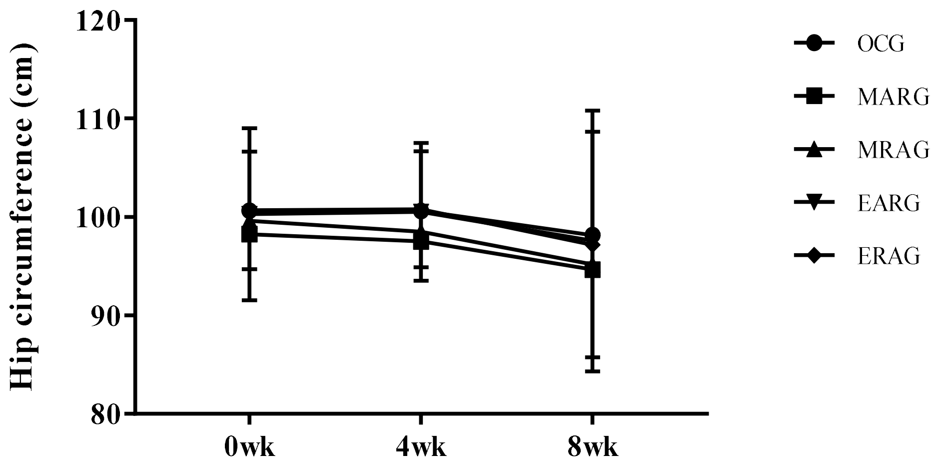

Figure 15. Change of hip circumference after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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⑧ Waist-hip ratio

<Table 18>, <Table 19> and <Figure 16> show the results of waist-hip ratio changes in obese women after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 18> shows the descriptive statistics of waist-hip ratio and one-way ANOVA after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 19> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and the period. There was no significant difference in the interaction effect between group and period (F=1.422, p=.213) and between groups (F=.183, p=.943); however, a significant difference was noted between periods (F=7.515, p=.002).

Table 18. The result of descriptive statistics and one-way ANOVA for waist-hip ratio by measurement trial (%)

Group	0wk	4wk	8wk	Total
OCG[1]	0.82±0.08	0.83±0.08	0.81±0.07	0.82±0.08
MARG[2]	0.82±0.06	0.81±0.04	0.79±0.03	0.80±0.04
MRAG[3]	0.82±0.04	0.80±0.05	0.81±0.08	0.81±0.06
EARG[4]	0.84±0.07	0.82±0.06	0.78±0.08	0.81±0.07
ERAG[5]	0.81±0.06	0.79±0.05	0.79±0.04	0.80±0.05
Total	0.82±0.06	0.81±0.06	0.80±0.06	0.81±0.18
F	.215	.450	.396	
p	.929	.772	.810	

Mean±standard deviation
OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 19. The result of two-way repeated ANOVA for waist-hip ratio

Variable	SS	df	MS	F	p	η^2	β
Between Subject							
Group	.009	4	.002	.183	.943	.018	.085
Error	.460	39	.012				
Within Subject							
Period	.014	1.705	.008	7.515	.002	.162	.904
Group×Period	.010	6.820	.002	1.422	.213	.127	.552
Error	.071	66.491	.001				

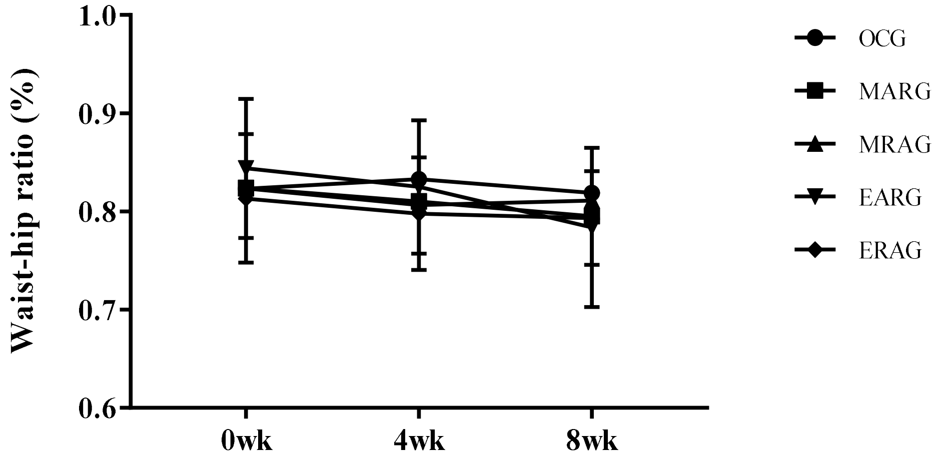

Figure 16. Change of waist-hip ratio after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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2) Physical fitness

(1) Grip strength

<Table 20>, <Table 21> and <Figure 17> show the results of grip strength changes in obese women after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 20> shows the descriptive statistics of grip strength and one-way ANOVA after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 21> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and the period. There was no significant difference in the interaction effect between group and period (F=1.018, p=.430) and between groups (F=.340, p=.850); however, a significant difference was noted between periods (F=4.034, p=.022).

Table 20. The result of descriptive statistics and one-way ANOVA for grip strength by measurement trial (kg)

Group	0wk	4wk	8wk	Total
OCG[1]	23.95±2.65	25.56±2.84	24.03±2.83	24.51±2.78
MARG[2]	24.69±5.23	24.85±4.51	25.98±3.89	25.17±4.41
MRAG[3]	25.63±2.81	26.95±2.36	26.91±2.60	26.50±2.57
EARG[4]	25.46±6.51	26.73±7.55	26.64±6.05	26.28±6.46
ERAG[5]	25.75±4.99	25.71±4.49	26.46±5.89	25.97±4.97
Total	25.07±4.41	25.96±4.43	25.94±4.36	25.86±4.40
F	.264	.304	.654	
p	.899	.873	.628	

Mean±standard deviation
OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 21. The result of two-way repeated measures ANOVA for grip strength

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	76.013	4	19.003	.340	.850	.034	.118
Error	2182.596	39	55.964				
Within Subject							
Period	22.893	2	11.447	4.034	.022	.094	.704
Group×Period	23.111	8	2.889	1.018	.430	.095	.441
Error	221.300	78	2.837				

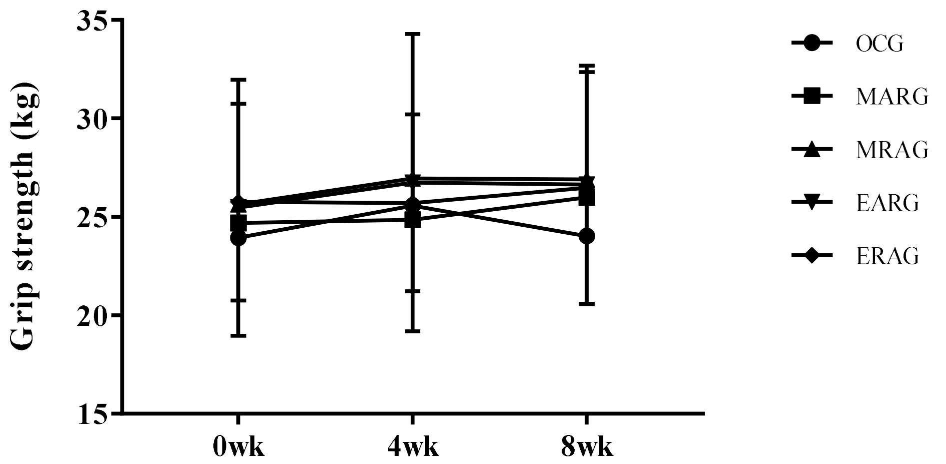

Figure 17. Change of grip strength after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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(2) Back strength

<Table 22>, <Table 23> and <Figure 18> show the results of back strength changes in obese women after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 22> shows the descriptive statistics of back strength and one-way ANOVA after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 23> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and the period. There was no significant difference in the interaction effect between group and period (F=1.190, p=.322) and between groups (F=.426, p=.789); however, a significant difference was noted between periods (F=17.978, p=.001).

Table 22. The result of descriptive statistics and one-way ANOVA for back strength by measurement trial (kg)

Group	0wk	4wk	8wk	Total
OCG[1]	55.31±13.11	60.09±10.92	60.51±7.12	58.64±10.57
MARG[2]	48.78±13.79	57.28±12.83	60.85±13.03	55.63±13.65
MRAG[3]	58.09±16.23	64.12±11.67	69.46±10.82	63.89±13.47
EARG[4]	52.43±16.88	61.41±20.33	70.53±19.34	61.46±19.58
ERAG[5]	57.29±27.24	68.21±25.55	63.51±19.41	63.00±23.79
Total	54.57±17.66	62.30±16.73	64.84±14.46	60.57±16.82
F	.369	.512	.727	
p	.829	.727	.458	

Mean±standard deviation

OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 23. The result of two-way repeated measures ANOVA for back strength

Variable	SS	df	MS	F	p	η^2	β
Between Subject							
Group	1137.195	4	293.299	.426	.789	.042	.138
Error	26855.365	39	688.599				
Within Subject							
Period	2640.821	1.648	1602.810	17.978	.001	.316	.999
Group×Period	699.138	6.590	106.083	1.190	.322	.109	.457
Error	5728.822	64.257	89.155				

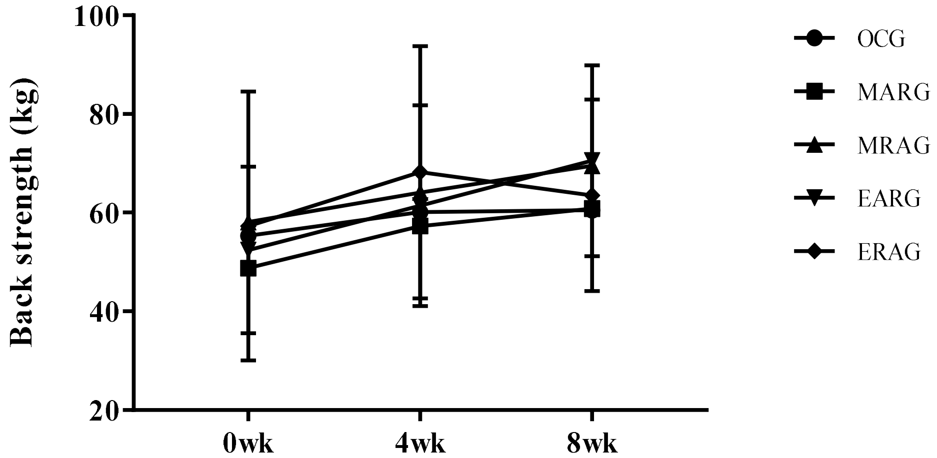

Figure 18. Change of back strength after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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(3) Sit-up

<Table 24>, <Table 25> and <Figure 19> show the results of sit-up changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 24> shows the descriptive statistics of sit-ups and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 25> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and the time period. There was no significant difference in the interaction effect between group and period (F=1.820, p=.086) and between groups (F=1.833, p=.142); however, a significant difference was noted between periods (F=18.173, p=.001). After examining the group change in detail, no significant difference was noted between the groups at 0 week (F=.800, p=.533) and 4 weeks (F=1.276, p=.296), but was observed at 8 weeks (F=4.311, p=.006). After post-hoc examination, EARG showed higher results than OCG.

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Table 24. The result of descriptive statistics and one-way ANOVA for sit-up by measurement trial (reps/60s)

Group	0wk	4wk	8wk	Total
OCG[1]	15.00±9.32	15.88±8.77	15.66±8.09	15.51±8.44
MARG[2]	18.87±6.03	20.00±4.03	22.00±5.90	20.29±5.32
MRAG[3]	15.62±8.88	17.25±6.51	19.62±6.99	17.50±7.43
EARG[4]	22.25±8.90	24.87±11.40	29.25±6.92	25.45±9.32
ERAG[5]	16.77±13.05	19.55±11.49	25.27±8.87	20.53±11.41
Total	17.51±9.50	19.29±9.04	22.06±8.57	19.62±9.03
F	.800	1.276	4.311	
p	.533	.296	.006	
Scheffe			1<4	

Mean±standard deviation
OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

Table 25. The result of two-way repeated measures ANOVA for sit-up

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	1477.531	4	369.383	1.833	.142	.158	.506
Error	7857.954	39	201.486				
Within Subject							
Period	481.949	2	240.974	18.173	.001	.318	1.000
Group×Period	193.053	8	24.132	1.820	.086	.157	.736
Error	1034.269	78	13.260				

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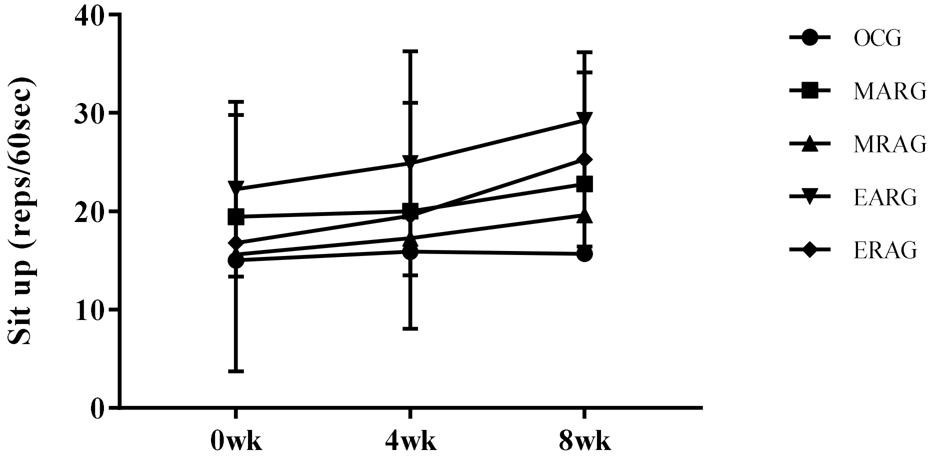

Figure 19. Change of sit-up after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

(4) Sit and reach

<Table 26>, <Table 27> and <Figure 20> show the results of sit and reach changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 26> shows the descriptive statistics of sit and reach and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 27> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and period. There was no significant difference in the interaction effect between group and period (F=2.167, p=.053) and between groups (F=.408, p=.802), however, a significant difference was noted between periods (F=14.367, p=.001).

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Table 26. The result of descriptive statistics and one-way ANOVA for sit and reach by measurement trial (cm)

Group	0wk	4wk	8wk	Total
OCG[1]	11.06±8.96	11.17±8.86	11.30±8.71	11.09±8.53
MARG[2]	11.34±11.19	12.67±9.29	14.38±8.93	12.80±9.50
MRAG[3]	14.28±7.04	15.25±7.00	16.64±6.01	15.39±6.51
EARG[4]	8.08±7.69	11.49±7.19	12.89±6.51	10.82±7.13
ERAG[5]	10.54±12.36	10.60±12.83	11.68±12.43	10.94±12.06
Total	11.12±9.40	12.22±9.03	13.26±8.69	12.19±9.04
F	.449	.355	.591	
p	.772	.839	.671	

Mean±standard deviation

OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

Table 27. The result of two-way repeated measures ANOVA for sit and reach

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	409.352	4	102.338	.408	.802	.040	.134
Error	9781.391	39	250.805				
Within Subject							
Period	111.890	1.636	68.374	14.367	.001	.269	.995
Group×Period	67.499	6.546	10.312	2.167	.053	.182	.755
Error	303.727	78	3.894				

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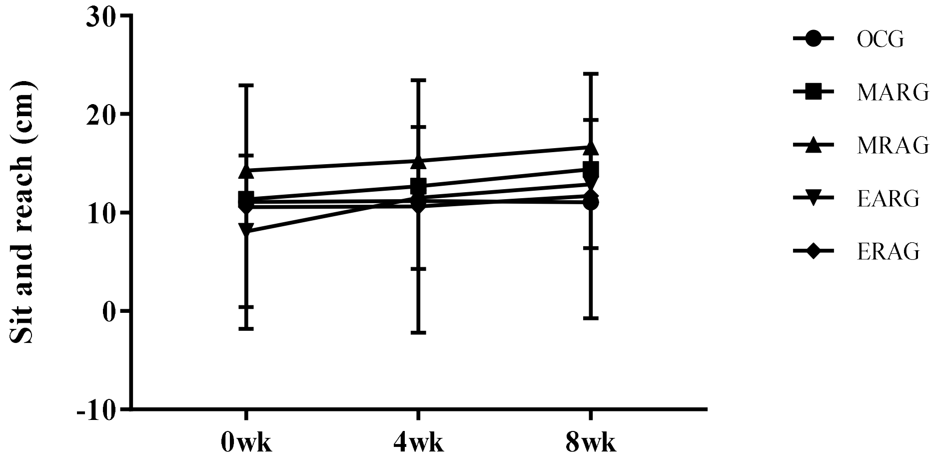

Figure 20. Change of sit and reach after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

(5) Physical efficiency index

<Table 28>, <Table 29> and <Figure 21> show the results of physical efficiency index changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 28> shows the descriptive statistics of physical efficiency index and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 29> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and period. There was no significant difference in the interaction effect between group and period (F=.506, p=.809) and between groups (F=1.018, p=.410), however, a significant difference was noted between periods (F=4.559, p=.021).

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Table 28. The result of descriptive statistics and one-way ANOVA for physical efficiency index by measurement trial (score)

Group	0wk	4wk	8wk	Total
OCG[1]	47.22±2.75	47.48±3.03	47.21±2.86	47.30±2.78
MARG[2]	46.90±2.17	48.12±3.20	47.34±4.90	47.45±3.48
MRAG[3]	47.28±2.14	49.44±1.73	49.12±2.30	48.61±2.21
EARG[4]	46.54±1.89	49.11±6.15	48.78±3.90	48.15±4.31
ERAG[5]	44.68±4.44	46.08±5.20	46.86±5.62	45.87±4.99
Total	46.53±2.90	48.01±4.10	47.84±3.98	47.46±3.66
F	1.268	.950	.552	
p	.299	.445	.698	

Mean±standard deviation
OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

Table 29. The result of two-way repeated measures ANOVA for physical efficiency index

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	115.885	4	28.971	1.018	.410	.095	.291
Error	1109.812	39	28.457				
Within Subject							
Period	60.422	1.567	38.567	4.559	.021	.105	.682
Group×Period	26.802	6.267	4.277	.506	.809	.049	.193
Error	516.835	61.100	8.459				

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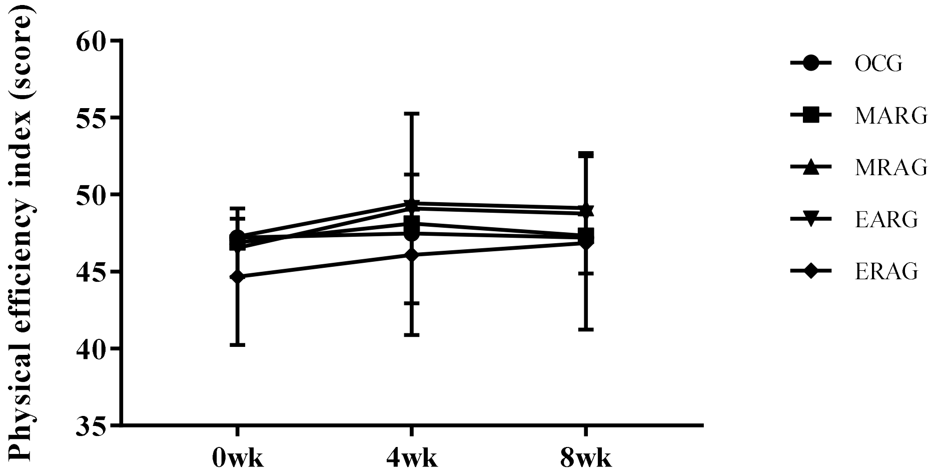

Figure 21. Change of physical efficiency index after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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3) Obesity-related cardiovascular disease risk factors

(1) Total cholesterol

<Table 30>, <Table 31> and <Figure 22> show the results of total cholesterol changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 30> shows the descriptive statistics of total cholesterol and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 31> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and period. There was no significant difference in the interaction effect between group and period (F=.840, p=.571) and between groups (F=.992, p=.423), however, a significant difference was noted between periods (F=7.047, p=.002).

Table 30. The result of descriptive statistics and one-way ANOVA for total cholesterol by measurement trial (mg/dL)

Group	0wk	4wk	8wk	Total
OCG[1]	195.22±23.43	199.11±19.62	194.03±29.60	196.12±23.80
MARG[2]	237.62±68.80	239.62±48.16	193.37±33.53	223.54±54.44
MRAG[3]	211.37±49.44	224.87±29.46	193.00±46.18	209.75±43.04
EARG[4]	226.25±72.78	222.75±26.42	209.00±40.01	219.33±48.68
ERAG[5]	224.77±56.51	223.22±15.64	206.66±26.48	218.22±36.65
Total	217.92±54.96	220.97±30.97	199.00±34.70	212.63±40.20
F	.780	2.262	.423	
p	.545	.080	.791	

Mean±standard deviation
OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 31. The result of two-way repeated measures ANOVA for total cholesterol

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	13179.658	4	3294.914	.992	.423	.092	.284
Error	129501.304	39	3320.546				
Within Subject							
Period	13354.706	2	6677.353	7.047	.002	.153	.920
Group×Period	6365.813	8	795.727	.840	.571	.079	.363
Error	73908.145	78	947.540				

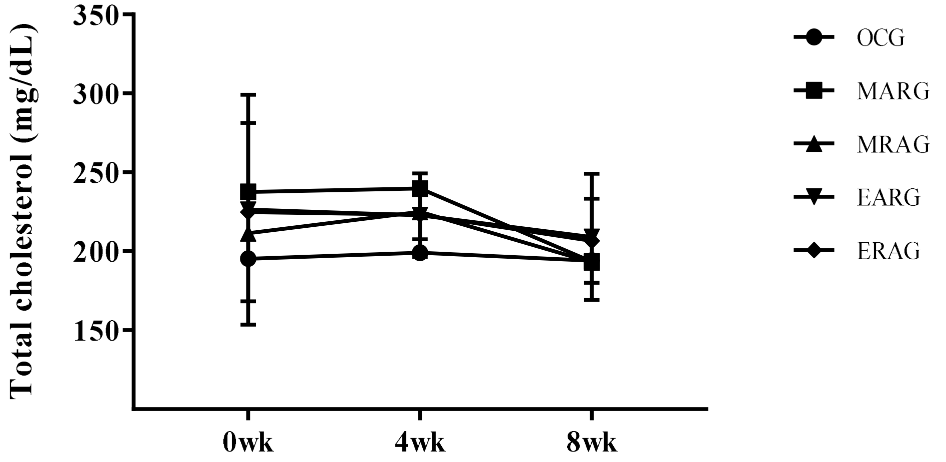

Figure 22. Change of total cholesterol after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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(2) Triglyceride

<Table 32>, <Table 33> and <Figure 23> show the results of triglyceride changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 32> shows the descriptive statistics of triglyceride and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 33> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and period. There was no significant difference in the interaction effect between group and period (F=1.106, p=.369) and between groups (F=1.339, p=.273), also, no significant difference was noted between periods (F=.211, p=.773).

Table 32. The result of descriptive statistics and one-way ANOVA for triglyceride by measurement trial (mg/dL)

Group	0wk	4wk	8wk	Total
OCG[1]	167.11±66.22	175.33±54.40	152.55±81.55	165.00±66.60
MARG[2]	175.37±73.86	195.12±86.32	141.37±63.87	170.62±75.39
MRAG[3]	210.50±96.52	177.37±49.87	209.48±86.86	199.12±78.73
EARG[4]	146.62±96.06	131.12±32.26	172.12±68.73	149.95±69.72
ERAG[5]	145.00±97.30	126.88±46.28	144.22±87.25	138.70±77.37
Total	169.24±85.94	161.40±59.94	164.02±79.36	164.88±75.08
F	.835	2.486	1.128	
p	.511	.059	.358	

Mean±standard deviation

OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 33. The result of two-way repeated measures ANOVA for triglyceride

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	56292.215	4	14073.054	1.339	.273	.121	.378
Error	409764.135	39	10506.773				
Within Subject							
Period	1347.750	1.688	798.53	.211	.773	.005	.080
Group×Period	28219.078	6.751	4179.889	1.106	.369	.102	.432
Error	248659.998	65.824	3777.664				

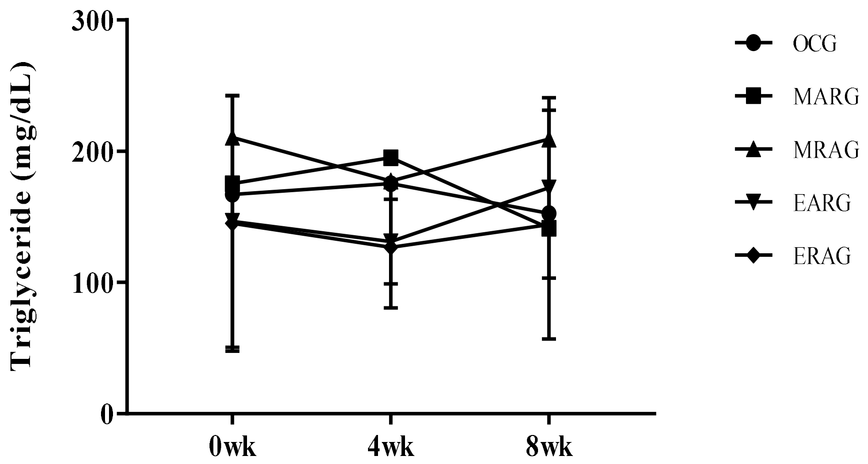

Figure 23. Change of triglyceride after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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(3) High-density lipoprotein cholesterol

<Table 34>, <Table 35> and <Figure 24> show the results of high-density lipoprotein cholesterol changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 34> shows the descriptive statistics of high-density lipoprotein cholesterol and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 35> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and period. There was no significant difference in the interaction effect between group and period (F=.915, p=.491), however, a significant difference were noted between between groups (F=2.932, p=.033) and periods (F=8.188, p=.002).

Table 34. The result of descriptive statistics and one-way ANOVA for high-density lipoprotein cholesterol by measurement trial (mg/dL)

Group	0wk	4wk	8wk	Total
OCG[1]	54.66±11.74	62.22±14.71	59.44±15.83	58.77±14.06
MARG[2]	60.25±8.41	78.62±19.36	74.37±19.07	71.08±17.63
MRAG[3]	50.87±13.16	60.75±10.63	59.87±15.34	57.16±13.46
EARG[4]	64.62±20.96	64.87±16.69	70.62±6.63	66.70±15.49
ERAG[5]	69.11±18.07	73.05±15.16	76.00±15.36	72.72±15.88
Total	59.67±15.82	67.60±16.19	47.66±16.10	58.31±16.03
F	2.154	2.115	2.500	
p	.092	.097	.058	

Mean±standard deviation
OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 35. The result of two-way repeated measures ANOVA for high-density lipoprotein cholesterol

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	5386.354	4	1346.589	2.932	.033	.231	.735
Error	17909.798	39	459.226				
Within Subject							
Period	1901.613	1.512	1257.604	8.188	.002	.174	.903
Group×Period	580.016	6.048	140.537	.915	.491	.086	.334
Error	9057.573	58.972	153.592				

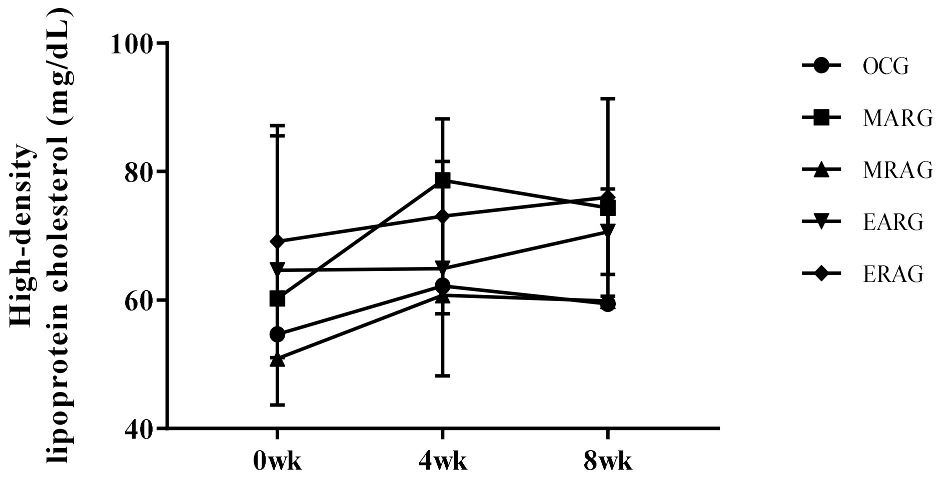

Figure 24. Change of high-density lipoprotein cholesterol after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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(4) Low-density lipoprotein cholesterol

<Table 36>, <Table 37>, and <Figure 25> show the results of low-density lipoprotein cholesterol changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 36> shows the descriptive statistics of low-density lipoprotein cholesterol and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 37> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and period. There was no significant difference in the interaction effect between group and period (F=1.415, p=.204) and between groups (F=1.244, p=.308), also, no significant difference was noted between periods (F=2.667, p=.076).

Table 36. The result of descriptive statistics and one-way ANOVA for low-density lipoprotein cholesterol by measurement trial (mg/dL)

Group	0wk	4wk	8wk	Total
OCG[1]	100.00±25.15	100.88±26.18	83.13±28.12	94.67±26.89
MARG[2]	121.75±53.21	125.80±46.86	104.85±32.43	117.46±44.00
MRAG[3]	109.12±46.95	129.50±31.52	96.45±35.76	111.69±39.62
EARG[4]	116.37±38.14	124.65±27.05	127.20±66.86	122.74±45.26
ERAG[5]	104.16±21.61	119.88±31.20	126.82±32.04	116.95±25.37
Total	109.65±37.29	119.47±31.20	106.75±42.52	111.95±37.00
F	.468	1.291	2.054	
p	.759	.290	.106	

Mean±standard deviation

OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 37. The result of two-way repeated measures ANOVA for low-density lipoprotein cholesterol

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	13157.503	4	3289.376	1.244	.308	.113	.352
Error	103110.687	39	2643.864				
Within Subject							
Period	3773.003	2	1886.502	2.667	.076	.064	.515
Group×Period	8006.182	8	1000.773	1.415	.204	.127	.602
Error	55168.117	78	707.284				

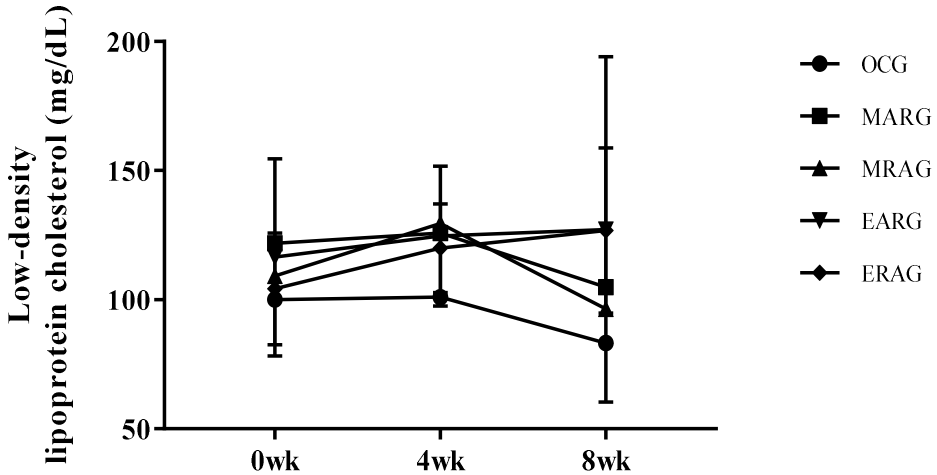

Figure 25. Change of low-density lipoprotein cholesterol after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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(5) Fasting glucose

<Table 38>, <Table 39> and <Figure 26> show the results of fasting glucose changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 38> shows the descriptive statistics of fasting glucose and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 39> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and period. There was no significant difference in the interaction effect between group and period (F=.714, p=.678) and between groups (F=2.011, p=.112), also, no significant difference was noted between periods (F=1.611, p=.206).

Table 38. The result of descriptive statistics and one-way ANOVA for fasting glucose by measurement trial (mg/dL)

Group	0wk	4wk	8wk	Total
OCG[1]	99.66±7.64	96.88±6.52	101.77±15.88	99.44±10.66
MARG[2]	100.12±6.08	96.12±4.32	94.12±5.22	96.79±5.63
MRAG[3]	94.75±8.65	91.87±9.49	91.50±6.36	92.70±8.08
EARG[4]	94.50±7.52	92.25±9.13	91.75±8.39	92.83±8.09
ERAG[5]	93.77±7.77	94.77±7.93	92.22±6.88	93.59±7.32
Total	96.60±7.76	94.44±7.62	94.50±10.09	95.18±8.49
F	1.427	.761	1.916	
p	.243	.557	.127	

Mean±standard deviation
OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 39. The result of two-way repeated measures ANOVA for fasting glucose

Variable	SS	df	MS	F	p	η^2	β
Between Subject							
Group	973.079	4	243.270	2.011	.112	.171	.549
Error	4716.769	39	120.943				
Within Subject							
Period	145.710	2	72.855	1.611	.206	.040	.316
Group×Period	258.437	8	32.305	.714	.678	.068	.308
Error	3528.343	78	45.235				

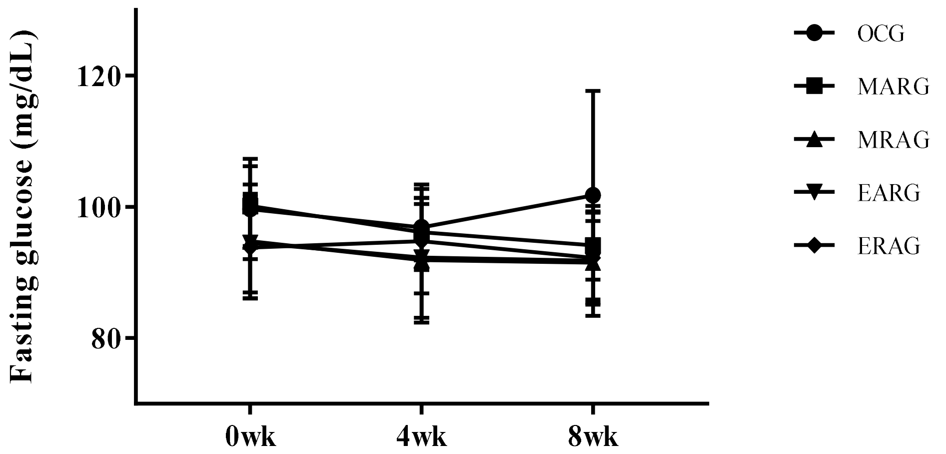

Figure 26. Change of fasting glucose after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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4) Upper extremity muscle function

(1) Front abdominal power test

<Table 40>, <Table 41> and <Figure 27> show the results of front abdominal power test changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 40> shows the descriptive statistics of front abdominal power test and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 41> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and period. There was a significant difference in the interaction effect between group and period (F=2.578, p=.015) and between periods (F=15.189, p=.001), however, no significant difference was noted between groups (F=.247, p=.910).

Table 40. The result of descriptive statistics and one-way ANOVA for front abdominal power test by measurement trial (cm)

Group	0wk	4wk	8wk	Total
OCG[1]	1796.11±678.29	1873.88±671.19	1749.44±740.90	1806.48±675.04
MARG[2]	1506.25±530.31	1951.25±836.46	2083.12±810.48	1846.87±749.68
MRAG[3]	1683.12±514.12	2150.00±491.01	2165.00±501.82	1999.37±533.82
EARG[4]	1767.50±576.95	2111.87±603.28	2253.43±755.89	2044.27±655.30
ERAG[5]	1988.88±896.22	1923.88±786.95	2126.38±766.03	2013.05±790.98
Total	1754.52±647.56	1997.92±663.24	2063.85±709.62	1938.76±673.47
F	.604	.282	.677	
p	.662	.888	.612	

Mean±standard deviation
OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 41. The result of two-way repeated measures ANOVA for front abdominal power test

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	1242977.515	4	310744.379	.247	.910	.025	.098
Error	48999536.31	39	1256398.367				
Within Subject							
Period	2574566.736	2	1287283.368	15.189	.001	.280	.999
Group×Period	1747946.597	8	218493.325	2.578	.015	.209	.893
Error	6610732.697	78	84752.983				

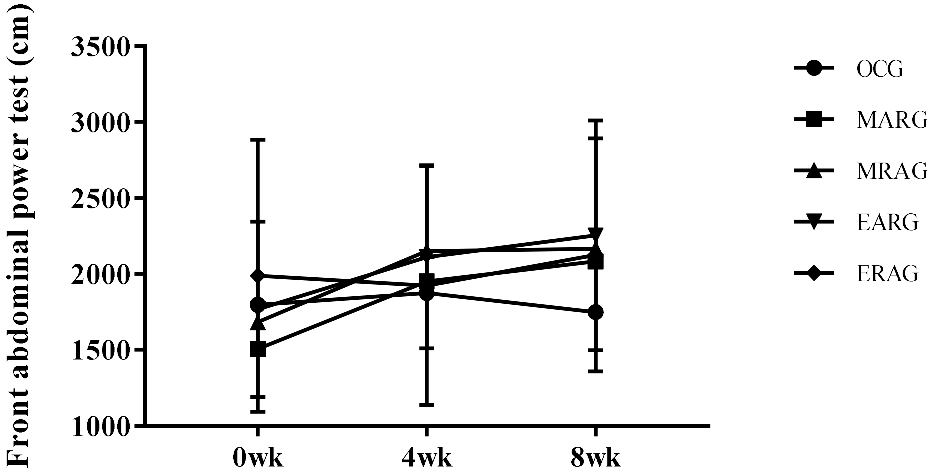

Figure 27. Change of front abdominal power test after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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(2) Left side abdominal power test

<Table 42>, <Table 43> and <Figure 28> show the results of left side abdominal power test changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 42> shows the descriptive statistics of left side abdominal power test and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 43> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and period. There was no significant difference in the interaction effect between group and period (F=1.392, p=.213) and between groups (F=1.033, p=.402), however, a significant difference was noted between periods (F=28.704, p=.001).

Table 42. The result of descriptive statistics and one-way ANOVA for left side abdominal power test by measurement trial (cm)

Group	0wk	4wk	8wk	Total
OCG[1]	1968.33±620.00	1996.11±405.12	2147.33±335.28	2037.25±459.91
MARG[2]	1998.75±460.51	2120.00±616.18	2470.00±670.91	2196.25±598.95
MRAG[3]	2095.00±668.77	2282.50±401.18	2538.75±396.60	2305.41±519.51
EARG[4]	2363.12±702.54	2466.25±728.90	2688.43±661.50	2505.93±681.41
ERAG[5]	2076.11±594.19	2491.66±579.78	2549.94±403.18	2372.57±555.25
Total	2093.59±602.60	2264.05±560.54	2466.79±512.79	2274.81±558.64
F	.535	1.385	1.517	
p	.711	.257	.216	

Mean±standard deviation

OCG[1], obesity control group; MARG[2], from aerobic to resistance exercise in the morning group; MRAG[3], from resistance to aerobic exercise in the morning group; EARG[4], from aerobic to resistance exercise in the evening group; ERAG[5], from resistance to aerobic exercise in the evening group; wk, week

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Table 43. The result of two-way repeated measures ANOVA for left side abdominal power test

Variable	SS	df	MS	F	p	η^2	β
Between Subject							
Group	3406466.315	4	851616.579	1.033	.402	.096	.295
Error	32149238.03	39	824339.437				
Within Subject							
Period	3141376.667	2	1570688.334	28.704	.001	.424	1.000
Group×Period	609154.254	8	76144.282	1.392	.213	.125	.593
Error	4268113.067	78	54719.398				

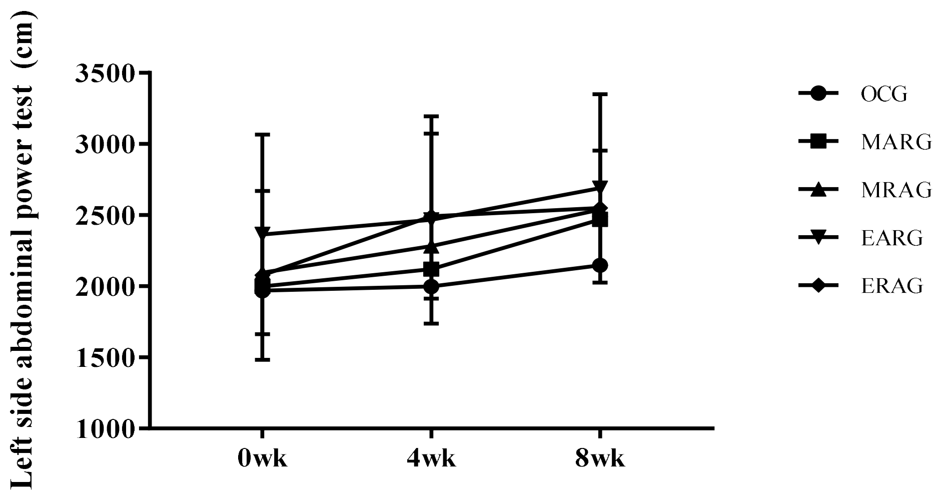

Figure 28. Change of left side abdominal power test after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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(3) Right side abdominal power test

<Table 44>, <Table 45> and <Figure 29> show the results of right side abdominal power test changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 44> shows the descriptive statistics of right side abdominal power test and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 45> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and period. There was no significant difference in the interaction effect between group and period (F=.244, p=.981) and between groups (F=1.371, p=.262), however, a significant difference was noted between periods (F=19.911, p=.001).

Table 44. The result of descriptive statistics and one-way ANOVA for right side abdominal power test by measurement trial (cm)

Group	0wk	4wk	8wk	Total
OCG[1]	1836.66±528.75	1937.77±491.98	2188.88±359.75	1987.77±474.05
MARG[2]	2096.25±456.10	2262.50±722.81	2490.00±662.26	2282.91±618.86
MRAG[3]	2063.75±570.83	2265.00±606.00	2432.87±470.75	2253.87±552.35
EARG[4]	2345.00±757.92	2652.00±849.12	2820.31±639.09	2605.77±747.65
ERAG[5]	2107.77±708.78	2230.00±672.95	2391.77±426.76	2243.18±603.33
Total	2078.19±605.87	2253.38±677.16	2449.84±531.53	2260.47±604.85
F	.777	1.271	1.723	
p	.547	.298	.164	

Mean±standard deviation
OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 45. The result of two-way repeated measures ANOVA for right side abdominal power test

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	5113745.168	4	1278436.292	1.371	.262	.123	.386
Error	36370278.86	37	932571.253				
Within Subject							
Period	3071778.561	2	1535889.280	19.911	.001	.338	1.000
Group×Period	15270.549	8	18783.819	.244	.981	.024	.120
Error	6016698.544	78	771373.161				

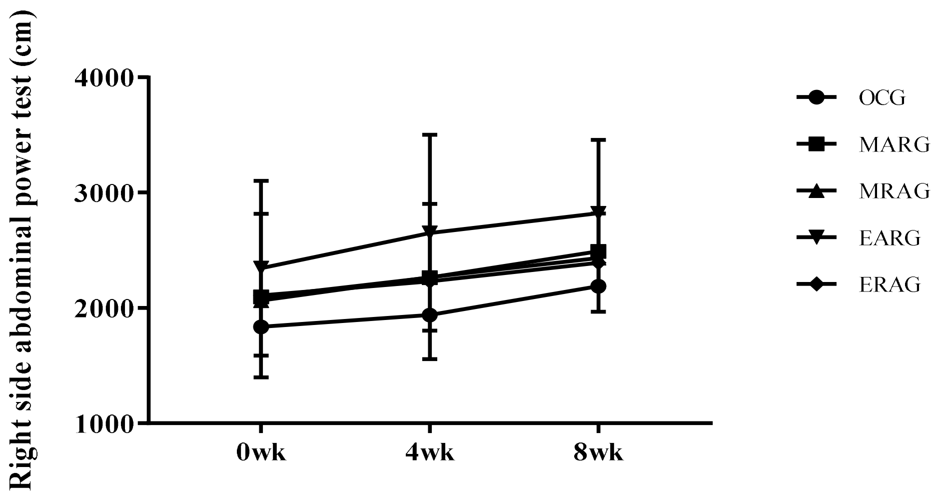

Figure 29. Change of right side abdominal power test after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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(4) Trunk flexor endurance test

<Table 46>, <Table 47> and <Figure 30> show the results of trunk flexor endurance test changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 46> shows the descriptive statistics of trunk flexor endurance test and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 47> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and period. There was significant difference in the interaction effect between group and period (F=3.382, p=.008) and between groups (F=3.114, p=.026), also, a significant difference was noted between periods (F=31.911, p=.001). After examining the group change in detail, no significant difference was noted between the groups at 0 week (F=.923, p=.460), but was observed at 4 weeks (F=3.012, p=.029) and 8 weeks (F=4.170, p=.007). After post-hoc examination, EARG showed higher results than OCG at 8 weeks.

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Table 46. The result of descriptive statistics and one-way ANOVA for trunk flexor endurance test by measurement trial (second)

Group	0wk	4wk	8wk	Total
OCG[1]	37.02±13.07	29.51±5.01	33.69±13.88	33.41±11.39
MARG[2]	46.40±26.11	75.63±25.80	88.65±39.00	70.23±34.62
MRAG[3]	34.93±15.81	47.12±24.48	66.73±30.62	49.60±26.98
EARG[4]	60.34±51.27	77.03±57.95	116.41±63.77	84.59±60.30
ERAG[5]	50.19±39.10	70.13±47.72	106.73±76.40	75.68±59.47
Total	45.23±31.48	58.45±39.55	80.42±56.18	61.36±42.40
F	.923	3.012	4.170	
p	.460	.029	.007	
Scheffe			1<4	

Mean±standard deviation
OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

Table 47. The result of two-way repeated measures ANOVA for trunk flexor endurance test

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	47559.869	4	11889.967	3.114	.026	.242	.764
Error	148889.857	39	3817.689				
Within Subject							
Period	29885.512	1.379	21676.928	31.911	.001	.450	1.000
Group×Period	12668.007	5.515	2297.129	3.382	.008	.258	.895
Error	36524.326	53.768	679.289				

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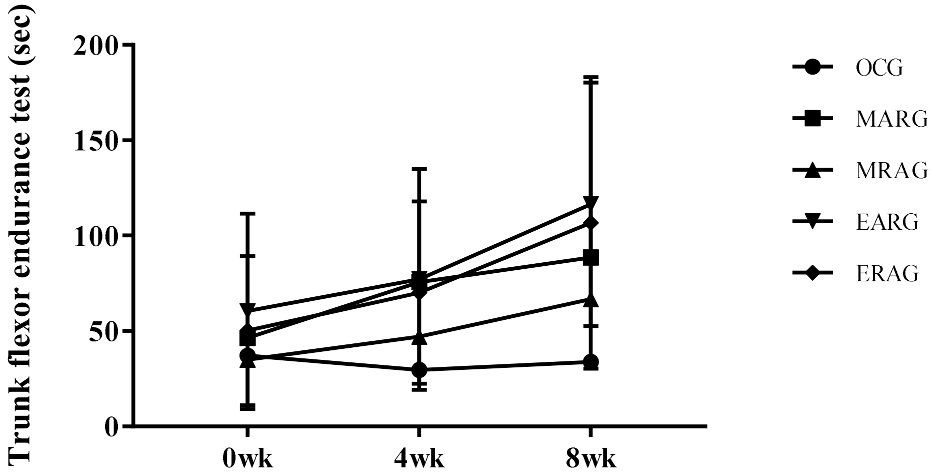

Figure 30. Change of trunk flexor endurance test after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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5) Lower extremity muscle function

(1) Vertical jump test

<Table 48>, <Table 49> and <Figure 31> show the results of vertical jump test changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 48> shows the descriptive statistics of vertical jump test and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 49> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and period. There was no significant difference in the interaction effect between group and period (F=1.084, p=.383) and between groups (F=.427, p=.788), however, a significant difference was noted between periods (F=10.763, p=.001).

Table 48. The result of descriptive statistics and one-way ANOVA for vertical jump test by measurement trial (cm)

Group	0wk	4wk	8wk	Total
OCG[1]	23.61±4.10	23.83±4.55	23.58±5.55	23.67±4.60
MARG[2]	23.62±3.17	25.75±3.33	25.75±2.76	25.04±3.13
MRAG[3]	23.43±2.73	23.93±1.92	25.68±2.83	24.35±2.62
EARG[4]	24.43±4.96	26.18±3.31	26.62±3.43	25.75±3.91
ERAG[5]	22.61±4.18	24.33±4.94	25.36±5.45	24.10±4.83
Total	23.52±3.76	24.73±3.75	25.32±4.21	24.52±3.90
F	.236	.696	.633	
p	.916	.600	.642	

Mean±standard deviation

OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

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Table 49. The result of two-way repeated measures ANOVA for vertical jump test

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	69.682	4	17.420	.427	.788	.042	.139
Error	1591.957	39	40.819				
Within Subject							
Period	78.598	1.683	46.705	10.763	.001	.216	.975
Group×Period	31.653	6.732	4.702	1.084	.383	.100	.422
Error	284.65	65.633	4.339				

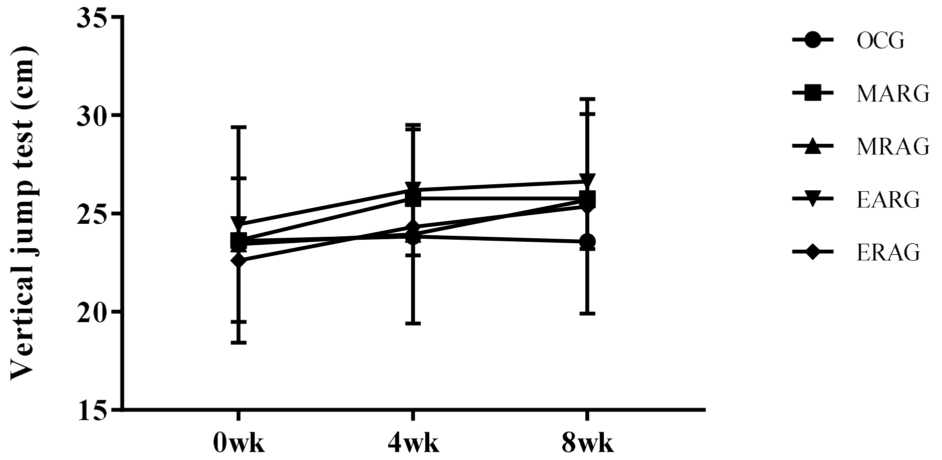

Figure 31. Change of vertical jump test after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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(2) Sit-to-stand

<Table 50>, <Table 51> and <Figure 32> show the results of sit-to-stand changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 50> shows the descriptive statistics of sit-to-stand and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 51> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and period. There was significant difference in the interaction effect between group and period (F=2.649, p=.013) and between periods (F=61.634, p=.001), however, no significant difference was noted between groups (F=2.405, p=.066). After examining the group change in detail, no significant difference was noted between the groups at 0 week (F=1.283, p=.293) and 4 weeks (F=2.449, p=.062), but was observed at 8 weeks (F=3.483, p=.016). After post-hoc examination, EARG showed higher results than OCG at 8 weeks.

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Table 50. The result of descriptive statistics and one-way ANOVA for sit-to-stand by measurement trial (reps/30second)

Group	0wk	4wk	8wk	Total
OCG[1]	24.66±5.51	25.66±5.09	26.85±5.16	25.72±5.15
MARG[2]	21.37±3.50	25.75±2.49	27.37±2.32	24.83±3.73
MRAG[3]	21.75±3.59	25.62±4.02	30.66±5.40	26.01±5.64
EARG[4]	25.50±5.45	31.62±6.69	34.62±4.68	30.58±6.66
ERAG[5]	23.88±4.59	27.88±4.59	31.55±6.28	27.91±5.87
Total	23.46±4.70	27.21±5.08	30.10±5.56	26.92±5.11
F	1.283	2.449	3.483	
p	.293	.062	.016	
Scheffe			1<4	

Mean±standard deviation

OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

Table 51. The result of two-way repeated measures ANOVA for sit-to-stand

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	511.227	4	127.807	2.405	.066	.198	.637
Error	2072.965	39	53.153				
Within Subject							
Period	1010.530	2	505.565	61.634	.001	.612	1.000
Group×Period	173.718	8	21.715	2.649	.013	.214	.902
Error	639.435	78	8.198				

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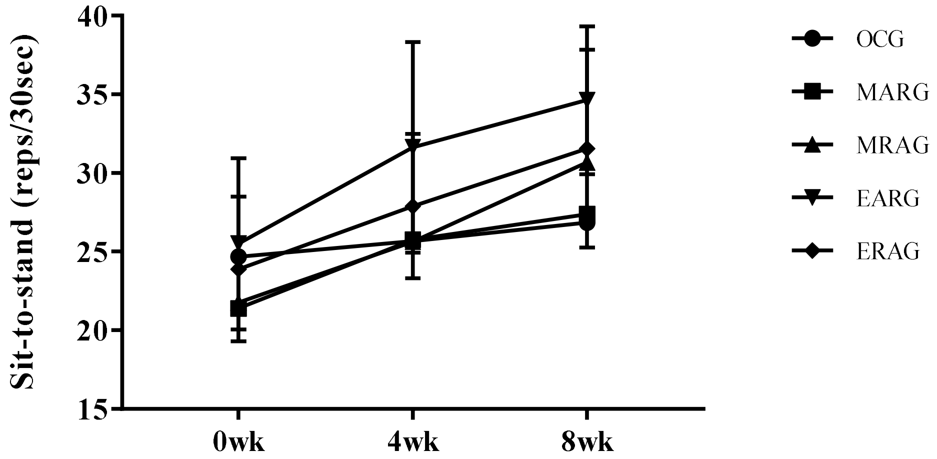

Figure 32. Change of sit-to-stand after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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6) **Sleep quality**

(1) Pittsburgh sleep quality index

<Table 52>, <Table 53> and <Figure 33> show the results of Pittsburgh sleep quality index changes in obese women after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 52> shows the descriptive statistics of Pittsburgh sleep quality index and one-way ANOVA results after participating in the 8 weeks combined exercise program according to the circadian rhythm and exercise order. <Table 53> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and period. There was significant difference in the interaction effect between group and period (F=2.650, p=.013). and between groups (F=4.897, p=.003), also, a significant difference was noted between periods (F=26.205, p=.001). After examining the group change in detail, no significant difference was noted between the groups at 0 week (F=1.897, p=.155), but was significant difference at 4 weeks (F=3.560, p=.014) and 8 weeks (F=9.742, p=.001). After post-hoc examination, all exercise groups showed lower results than OCG at 8 weeks.

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Table 52. The result of descriptive statistics and one-way ANOVA for Pittsburgh sleep quality index by measurement trial (score)

Group	0wk	4wk	8wk	Total
OCG[1]	7.66±1.49	7.50±1.58	7.66±1.41	7.61±1.44
MARG[2]	5.37±2.13	5.12±1.12	3.87±1.80	4.79±1.79
MRAG[3]	7.62±1.99	5.44±1.33	5.00±1.11	6.02±1.87
EARG[4]	6.50±1.69	5.12±1.24	4.37±1.40	5.33±1.65
ERAG[5]	6.88±2.57	5.66±2.39	4.77±1.48	5.74±2.25
Total	6.87±2.08	5.84±1.80	5.24±1.95	5.98±1.94
F	1.897	3.560	9.742	
p	.155	.014	.001	
Post-hoc			2,3,4,5<1	

Mean±standard deviation
OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

Table 53. The result of two-way repeated ANOVA for Pittsburgh sleep quality index

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	124.917	4	31.229	4.897	.003	.334	.934
Error	248.709	39	6.377				
Within Subject							
Period	62.292	2	31.146	26.205	.001	.402	1.000
Group×Period	25.201	8	3.150	2.650	.013	.214	.903
Error	92.707	78	1.189				

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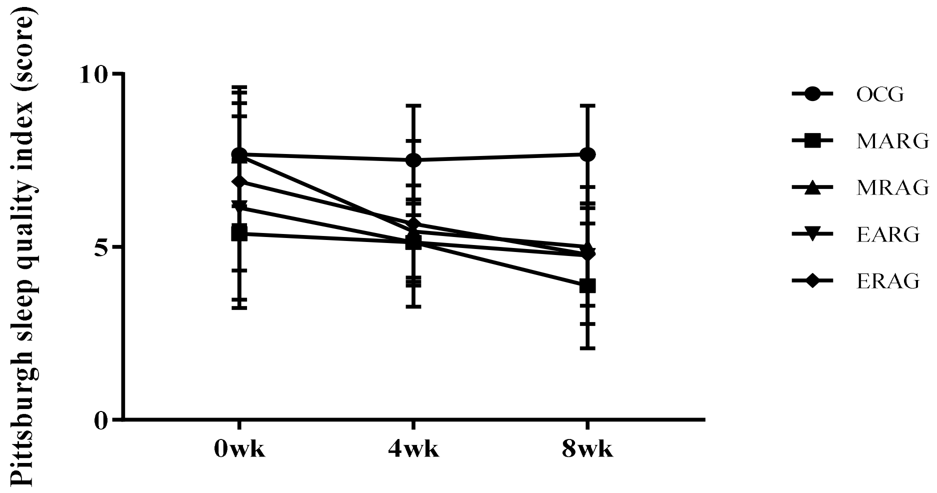

Figure 33. Change of Pittsburgh sleep quality index after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group; wk, week

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IV. Study Ⅱ: Effect of circadian rhythm and exercise order on skeletal muscle hypertrophy and mitochondrial biogenesis in rats with obesity

1. Research significance

Previous studies have reported that the circadian rhythm may alter the heart rate, body temperature, blood pressure, metabolic function, hormones, and exercise capacity (Serin & Tek, 2019). Testosterone was found to be highest in the afternoon, and it is recommended to exercise in the afternoon rather than in the morning to improve muscle strength (Küüsmaa et al., 2016). However, in the mornings individuals usually have a lower heart rate due to the circadian rhythm, and morning exercise may increase the levels of growth-related hormones (Haupt et al., 2021). Obesity is an emerging global problem that promotes the incidence of chronic diseases such as cardiovascular disease, diabetes, and cancer (Visscher & Seidell, 2001). Obesity is a form of excessive body fat accumulation due to the deposition of triglycerides and free fatty acids, which eventually leads to an increase in body weight and body mass index. Diet and exercise plans are used to manage obesity, and exercise effectively prevents obesity by increasing muscle mass as well as body fat mass, and muscle mass increases the basal metabolic rate (Speakman & Selman, 2003). Aerobic and resistance exercise can be used to prevent and manage obesity. Aerobic exercise effectively reduces fat mass by promoting the oxidation of fatty acids accumulated in the body. PGC-1α is a transcription coactivator that regulates the generation and function of mitochondria and is closely related to metabolic regulation (Liang & Ward, 2006). The PGC-1α expression increases endurance exercise capacity. Conversely, decreased PGC-1α is known to induce acute inflammation and decreased mitochondrial function along with decreased exercise capacity (Scarpulla, 2011; Traby & Langin, 2005). The expression level of PGC-1α is regulated by AMPK. Aerobic exercise upregulates

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AMPK to regulate mitochondrial biogenesis through the AMP/ATP balance and PGC-1α activity (Coffey & Hawley, 2007).

Resistance exercise has been reported to increase protein synthesis through the mTOR signaling pathway (Bodine, 2006). mTOR is classified into mTORC1 and mTORC2, and mTORC1 is known to be an important factor in regulating muscle mass in response to stimulation by nutrients, growth factors, and hormones. Resistance exercise performed in human and animal models upregulated the expression level of mTORC1. Increased mTORC1 phosphorylates Protein 70kD ribosomal protein S6 kinase (p70S6K) and induces muscle synthesis, emphasizing the importance of mTOR for muscle hypertrophy (Fyfe et al., 2016). Aerobic exercise, when performed after resistance exercise, increases the expression level of AMPK and represses mTORC1 expression, raising the problem of muscle hypertrophy signaling pathways (Atherton et al., 2005). Ogasawara et al. (2014) reported that Akt and mTOR phosphorylation levels did not differ with the exercise order; therefore, the mechanism of mTOR down-regulation must be reconfirmed. Exercise shows different effects depending on the exercise order and timing, which are difficult to determine. In addition, there were very few studies that used experimental animals to analyze the changes in signaling pathways related to muscle hypertrophy and mitochondrial biogenesis according to exercise order and timing. Thus, it was necessary to elucidate the mechanisms of changes in muscle hypertrophy and mitochondrial biogenesis after exercise according to the circadian rhythm and exercise order.

2. Research purpose

The purpose of this study II was to determine effect of 8 weeks of combined exercise according to circadian rhythm and exercise order on muscle hypertrophy, mitochondrial biogenesis and muscle cross-sectional area changes in obese rats.

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3. **Materials and methods**

1) Experimental animals

SD (Sprague-Dawley) rats (5 weeks old, female, n=30) were maintained on a high-fat diet (carbohydrates 20Kcal%, protein 20Kcal%, fat 60Kcal% feed; D12492, Rodent Diet Inc., NJ, USA) for 10 weeks to induce obesity. The rats were considered obese if their body weight increased by 20% or more compared to the body weight of rats that were fed the general diet (Commercial rat Chow, Samyang Co,. Korea) (Liao et al., 2021). The random assignment method was applied, and all experiment rats (n=30) divided into five groups: the obesity control group (OCG, n=6), aerobic-resistance exercise in the morning group (MARG, n=6), resistance-aerobic exercise in the morning group (MRAG, n=6), aerobic-resistance exercise in the evening group (EARG, n=6), resistance-aerobic exercise in the evening group (ERAG, n=6) (Table 54). Experimental procedures were conducted in accordance with the guidelines for the Care and Use of Laboratory Animals at Jeju National University. Animals were maintained at a constant room temperature of 22°C and 60% humidity under a 12/12-hr light-dark cycle. The use of rats in this study was approved by Ethical committee of Jeju National University (approval number: 2021-0052).

Table 54. Grouping of the experimental animal

8 weeks					
OCG (n=6)	MARG (n=6)	MRAG (n=6)	EARG (n=6)	ERAG (n=6)	Total (n=30)

OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistance-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group

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2) Experimental study design

This study was designed to investigate the effect of combined exercise according to circadian rhythm and exercise order on the molecular biology and histology in rats with obesity. All rats in this experiment had a treadmill exercise and ladder climb exercise adaptation period of 1 week. All the mice were sacrificed 48 hours after exercise for biochemical and histological analyses, and the tissues were prepared. The overall experimental design of this study is shown in <Figure 34>.

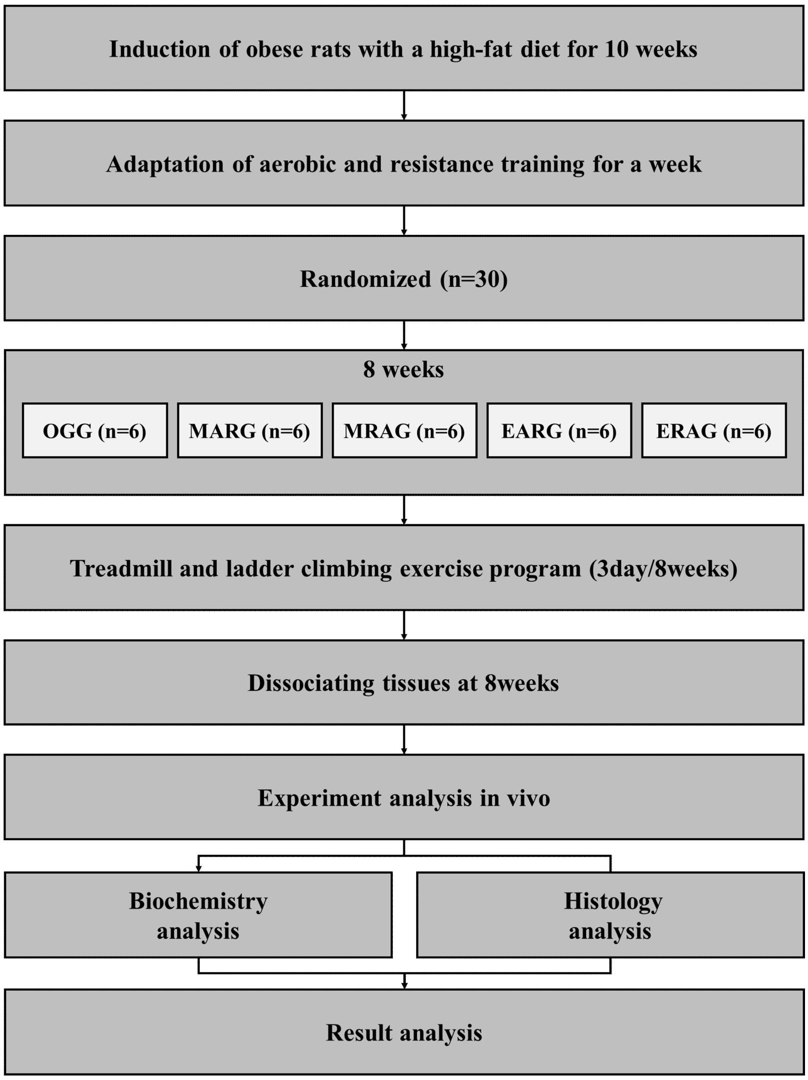

Figure 34. The experimental study design for study Ⅱ

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3) Combined exercise protocols

Combined exercises were performed at 7:00 AM and 7:00 PM for 8 weeks.

(1) Aerobic exercise

Aerobic exercise was performed based on the treadmill training protocol of Zhang et al. (2019). Moderate-intensity exercise on the treadmill device (JD-A-09 type, JEUNGDO Bio & Plant Co., Ltd., Korea) was comprised of walking at a speed of 14 to 16 m/min for 30 min, thrice a week for 8 weeks (Figure 35).

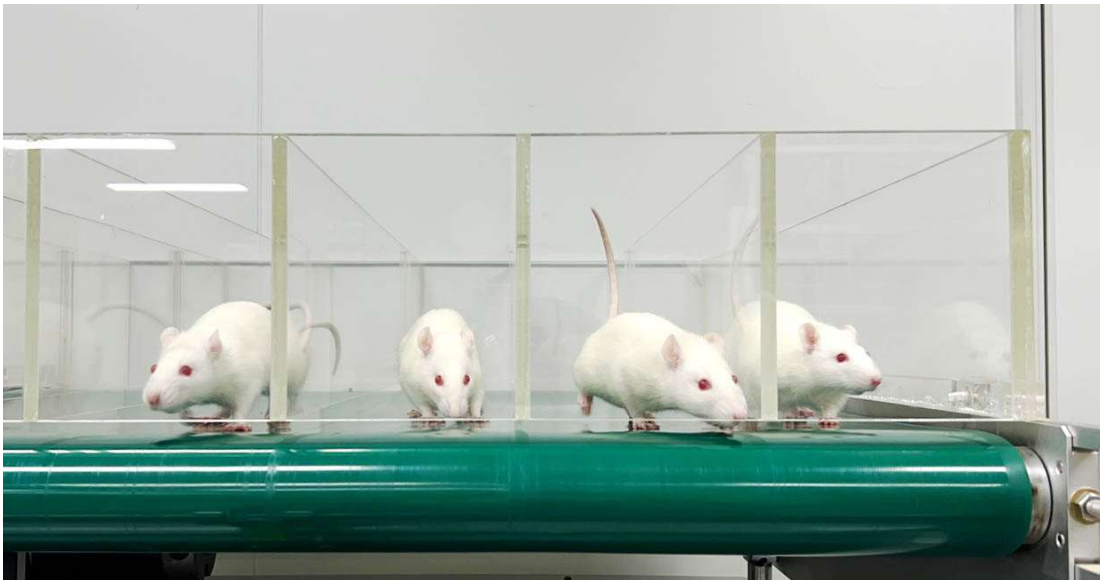

Figure 35. Treadmill exercise

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(2) Resistance exercise

For resistance exercise, the methods described by Cassilhas et al. (2012) and Keaemer et al. (2013) were used. For the ladder-climbing exercise, the rats climbed a ladder with a length of 1 m, interval of 2 cm, and angle of 80°, thrice a week for 8 weeks. The initial load was started at 50% of the animal body weight and gradually increased to 75%, 90%, and 100%. The rest time was set to 1 minute, and the exercise was continued until 8 climbs were completed or the entire length of the ladder could not be climbed. The weight was fixed to the proximal end of the rat tail using a swivel and tape (Figure 36).

Figure 36. Ladder-climbing exercise

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4) Sacrifice and tissue preparation

To perform histological and biochemical analyses on the tissues, the rat were sacrificed and excised 48 hours after the end of exercise. This study used the flexor pollicis longus and soleus muscles.

Experimental animals were sacrificed in a CO_2 chamber and pretreated with OCT combined (Tissue Tek; Sakura Finetek Europe B.V, Zoeterwoude, Netherlands) for the morphological analysis of muscles. The flexor pollicis longus and soleus muscles were stored at -80°C for further biochemical analyses.

5) Western blot

Protein lysates were extracted from the dissected flexor pollicis longus and soleus muscles. The tissues were introduced into triton lysis buffer, and the nucleus and cytoplasm were separated using the nuclear extraction and cytosol extraction buffers, respectively. Denatured proteins were separated on sodium dodecyl sulphate-polyacrylamide gel and then transferred onto polyvinylidene difluoride membrane on ice at 200mA for 2 hours. The membranes were blocked with 5% skim milk and washed with 0.1% Tween 20 in tris buffered saline for 30 min at room temperature. The membranes were incubated overnight at 4°C with primary antibodies.

Protein (20μg) was used for Western blot analysis. Anti-IGF-1 mouse monoclonal antibody (1:1,000, Santa Cruz Biotechnology, Santa Cruz, CA, USA), anti-PI3K mouse polyclonal antibody (1:1,000, Cell Signaling Biotechnology, Danvers, MA, USA), anti-phosphorylated mTOR rabbit polyclonal antibody (1:1,000, Cell Signaling Biotechnology, Danvers, MA, USA), anti-phosphorylated Akt rabbit polyclonal antibody (1:1,000, Cell Signaling Biotechnology), anti-phosphorylated ERK1/2 rabbit monoclonal antibody (1:1,000, Cell Signaling Biotechnology), anti-GAPDH mouse monoclonal antibody (1:1,000, Santa Cruz Biotechnology), anti-phosphorylated AMPK

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mouse polyclonal antibody (1:1,000, Cell Signaling Biotechnology), anti-PGC-1α mouse monoclonal antibody (1:1,000, Cell Signaling Biotechnology), anti-FNDC5 mouse polyclonal antibody (1:1,000, Cell Signaling Biotechnology), anti-β-Actin mouse polyclonal antibody (1:1,000, Cell Signaling Biotechnology), and goat anti-mouse or goat anti-rabbit horseradish peroxidase-conjugated secondary antibody (1:1,000, GeneTex Inc., Irvine, CA, USA) were used. The blotting proteins were detected using Westar ECL substrates (Cyanagen, Bologna, Italy). The protein density was analyzed using Chemidoc (Bio-Rad, Hercules, CA, USA). <Table 55> provides information on the types and ratios of primary and secondary antibodies used in this study.

Table 55. Skeletal muscle metabolism related protein and ratio

	Primary		Secondary	
	Antibody	Ratio	Antibody	Ratio
Muscle hypertrophy	IGF-1	1:1000	anti-Mouse	1:2000
	PI3K	1:1000	anti-Mouse	1:2000
	p-ERK	1:1000	anti-Rabbit	1:2000
	p-AKT	1:1000	anti-Rabbit	1:2000
	p-mTOR	1:1000	anti-Rabbit	1:2000
	GAPDH	1:1000	anti-Rabbit	1:2000
Mitochondria biogenesis	p-AMPK	1:1000	anti-Mouse	1:2000
	PGC1α	1:1000	anti-Mouse	1:2000
	Irsin/FNDC5	1:1000	anti-Mouse	1:2000
	β-Actin	1:1000	anti-Mouse	1:2000

IGF-1, Insulin like growth factor 1; PI3K, Phosphoinositide 3-kinases; p-ERK, Phosphorylated extracellular signal-regulated kinase 1/2; p-Akt, phosphorylated protein kinase B; p-mTOR, phosphorylated mammalian target of rapamycin; p-AMPK, Phosphorylated AMP-activated protein kinase; CaMK, calcium/calmodulin-dependent protein kinase type; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator1-alpha

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6) Immunofluorescence staining

To detect muscle hypertrophy in the flexor pollicis longus, tissues were embedded and frozen at 20°C. Cross sections (20µm) were made on a cryostat. Sections were fixed with 4% paraformaldehyde and 4% sucrose in PBS at room temperature for 40 min, permeabilized with 0.5% Nonidet P-40 in PBS, and blocked with 2.5% horse serum and 2.5% bovine serum albumin for 4 hr at room temperature. The sections were incubated with anti-neurofilament-200 (NF-200) rabbit polyclonal antibody (1:700) (Sigma-Aldrich, St. Louis, MO, USA). They were then incubated with rhodamine-goat anti-rabbit secondary antibody (1:600) (Molecular Probes, Eugene, OR, USA) and Hoechst (33342, 1:400, Sigma-Aldrich, Taufkirchen, Germany) for 1 h at room temperature. The stained samples were viewed with a fluorescence microscope (Nikon model E-600, Nikon, Kawasaki, Japan), and the images were captured with a digital camera, and analyzed using Adobe Photoshop Software (version CS6, San Jose, CA, USA). The myofiber cross-section area in the flexor pollicis longus muscle were evaluated using the i-Solution software (Image and Microscope Technology, Goleta, CA, USA).

7) Statistical analysis

All the data were presented as mean and standard. Statistical analysis was performed using one-way ANOVA analysis of all variances followed by Tukey post hoc test. The significance level was set at $p<0.05$. All graphs were drawn using Prism 6 (GraphPad, La Jolla, CA, USA).

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4. Results

1) Body weight

(1) Changes in body composition according to circadian rhythm and exercise order after combined exercise.

① Body weight

<Table 56>, <Table 57> and <Figure 37> show the results of body weight changes in obese rat after applying the 8 weeks combined exercise program according to the circadian rhythm and exercise order.

<Table 56> shows the descriptive statistics of body weight and one-way ANOVA results after participating in an 8-week combined exercise program according to the circadian rhythm and exercise order. <Table 57> shows the results of the two-way repeated measures ANOVA confirming the interaction effect between the group and the time period. There was significant difference in the interaction effect between group and period (F=6.806, p=.007), also, a significant difference was noted between groups (F=8.164, p=.003) and periods (F=15.478, p=.003). After performing the post-hoc test, all exercise groups was found to be lower than OCG at 8 weeks.

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Table 56. The result of descriptive statistics and one-way ANOVA for body weight by measurement trial (g)

Group	0wk	8wk	Total
OCG[1]	303.00±20.15	343.66±21.02	323.33±20.58
MARG[2]	276.66±8.75	295.33±11.01	285.995±9.88
MRAG[3]	278.30±13.63	271.33±11.71	274.815±12.67
EARG[4]	276.90±14.28	275.33±16.65	276.115±15.46
ERAG[5]	272.20±7.45	284.66±2.30	278.43±4.87
Total	281.41±16.18	294.06±29.54	287.73±22.86
F	2.438	13.034	
p	.115	.001	
Post-hoc		2,3,4,5<1	

Mean±standard deviation
OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group; wk, week

Table 57. The result of two-way repeated measures ANOVA for body weight

Variable	SS	df	MS	*F*	*p*	η^2	β
Between Subject							
Group	9951.849	4	2487.962	8.164	.003	.766	.965
Error	3047.413	10	304.741				
Within Subject							
Period	1200.801	1	1200.801	15.478	.003	.608	.942
Group×Period	2112.142	4	528.036	6.806	.007	.731	.927
Error	755.787	10	77.579				

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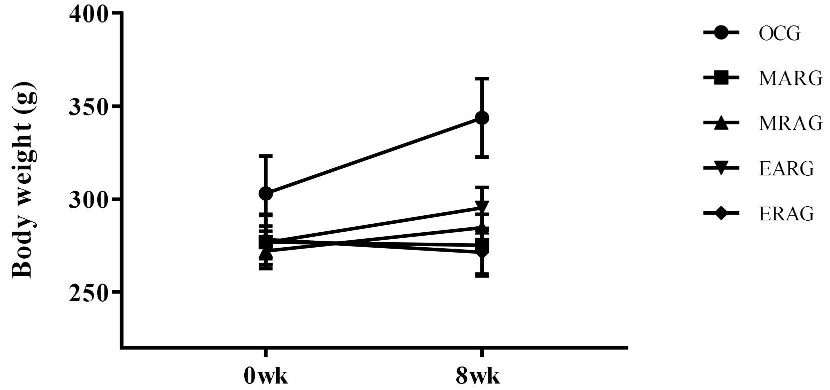

Figure 37. Change of body weight after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group

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2) Cross-sectional area of muscle

(1) Cross-sectional changes in the flexor pollicis longus muscle after 8 weeks of combined exercise program according to the circadian rhythm and exercise order.

<Table 58> and <Figure 38> show the results of cross-sectional changes in the flexor pollicis longus muscle after 8 weeks of combined exercise program according to the circadian rhythm and exercise order.

<Table 58> presents the descriptive statistics of the cross-sectional area of the flexor pollicis longus muscle after 8 weeks of combined exercise according to the circadian rhythm and exercise order and the results of one-way ANOVA. Using one-way ANOVA, a statistically significant difference was noted in the cross-sectional area of the flexor pollicis longus muscle (F=36.649, p=.001). After performing the post-hoc test, OCG, MRAG, ERAG, and EARG were found in the order.

Table 58. The result of descriptive statistics and one-way ANOVA for CSA of flexor pollicis longus muscle 8 weeks after combined exercise (㎛)

Group	OCG[1]	MARG[2]	MRAG[3]	EARG[4]	ERAG[5]	Total	*F*	*p*	*Tukey*
CSA	166.87±17.37	205.18±20.02	226.31±19.86	362.84±63.21	288.14±54.81	249.06±79.58	36.649	.001	1<3<5<4

Mean±standard deviation

CSA, cross sectional area; OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance- aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group

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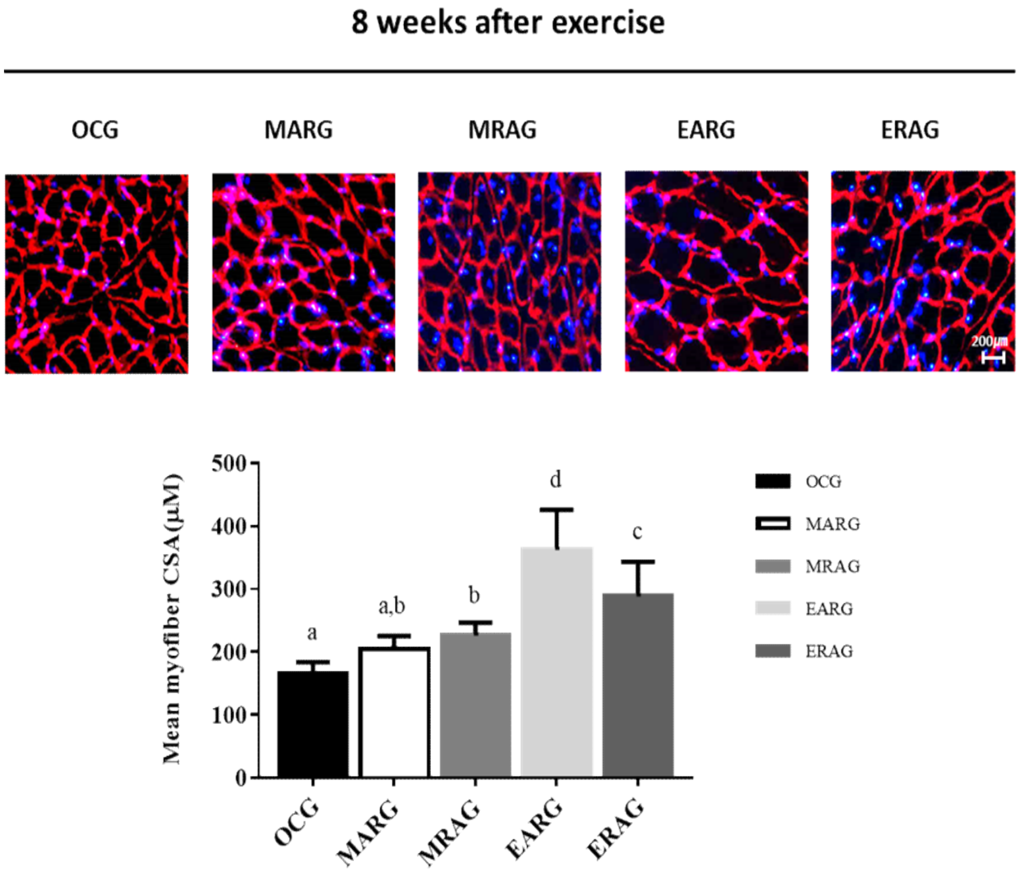

Figure 38. Exercise order and circadian rhythm regulated cross-sectional area of flexor pollicis longus muscle 8 weeks after combined exercise, immunofluorescence staining. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group

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3) Signaling pathway for muscle hypertrophy in flexor pollicis longus muscle

(1) Expression of IGF-1 in the flexor pollicis longus muscle after 8 weeks of combined exercise

<Table 59> and <Figure 39> show the results of expression of IGF-1 in the flexor pollicis longus muscle of obese rats after 8 weeks of combined exercise program according to circadian rhythm and exercise order.

<Table 59> shows the descriptive statistics of the IGF-1 expression level in the flexor pollicis longus muscle after 8 weeks of combined exercise program according to the circadian rhythm and exercise order and the results of one-way ANOVA. One-way ANOVA was used to confirm the difference between groups. The expression level of IGF-1 showed a statistically significant difference (F=24.499, p=.001). After performing the post-hoc test, MARG was found to be higher than OCG, and MRAG and EARG to be higher than MARG.

Table 59. The result of descriptive statistics and one-way ANOVA for IGF-1/GAPDH ratio in flexor pollicis longus muscle 8 weeks after combined exercise (%)

Group	OCG[1]	MARG[2]	MRAG[3]	EARG[4]	ERAG[5]	Total	*F*	*p*	*Tukey*
IGF-1	1.78±0.06	2.04±0.07	2.25±0.07	2.28±0.08	1.94±0.69	2.06±0.20	24.499	.001	1<2<3,4

Mean±standard deviation

IGF-1, Insulin-like growth factor - I; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance- aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group

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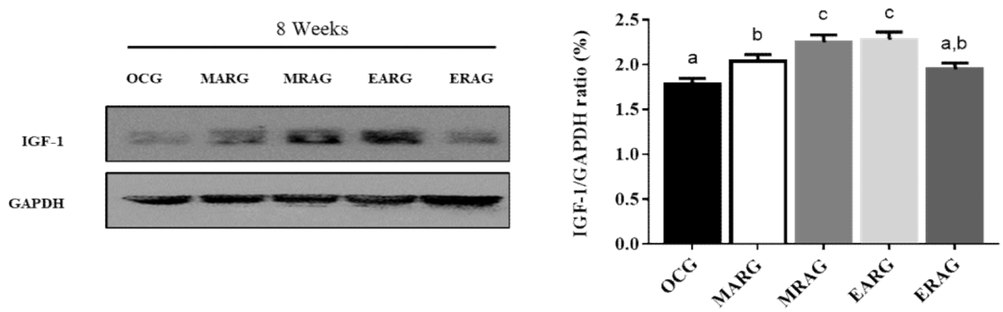

Figure 39. Exercise order and circadian rhythm regulated expression levels of IGF-1 in flexor pollicis longus muscle 8 weeks after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group

(2) Expression of PI3K in the flexor pollicis longus muscle after 8 weeks of combined exercise

<Table 60> and <Figure 40> show the results of expression of PI3K in the flexor pollicis longus muscle of obese rats after 8 weeks of combined exercise program according to circadian rhythm and exercise order.

<Table 60> shows the descriptive statistics of the PI3K expression level in the flexor pollicis longus muscle after 8 weeks of combined exercise program according to the circadian rhythm and exercise order and the results of one-way ANOVA. One-way ANOVA was used to confirm the difference between groups. The expression level of PI3K showed a statistically significant difference (F=112.383, p=.001). After performing the post-hoc test, MARG was found to be higher than OCG, and MRAG to be MARG higher than. in addtion, EARG and ERAG was found to be higher than MRAG.

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Table 60. The result of descriptive statistics and one-way ANOVA for PI3K/GAPDH ratio in flexor pollicis longus muscle 8 weeks after combined exercise (%)

Group	OCG[1]	MARG[2]	MRAG[3]	EARG[4]	ERAG[5]	Total	*F*	*p*	*Tukey*
PI3K	0.11±0.03	0.20±0.01	0.28±0.01	0.47±0.02	0.42±0.02	0.29±0.14	112.383	.001	1<2<3<4,5

Mean±standard deviation

PI3K, phosphatidylinositol 3-kinase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance- aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group

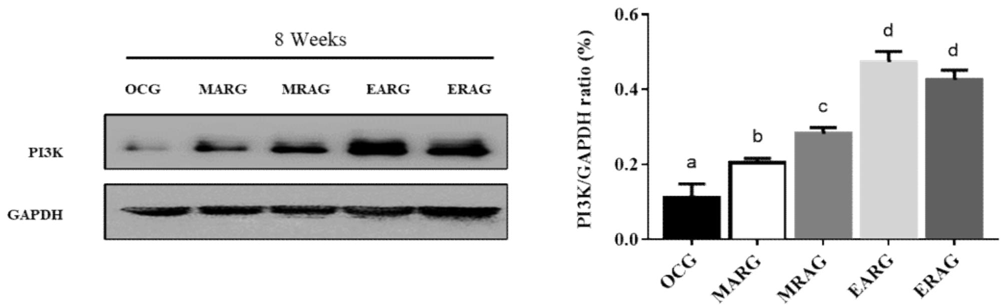

Figure 40. Exercise order and circadian rhythm regulated expression levels of PI3K in flexor pollicis longus muscle 8 weeks after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group

(3) Expression of p-Akt in the flexor pollicis longus muscle after 8 weeks of combined exercise

<Table 61> and <Figure 41> show the results of expression of p-Akt in the flexor pollicis longus muscle of obese rats after 8 weeks of combined exercise program according to circadian rhythm and exercise order.

<Table 61> shows the descriptive statistics of the p-Akt expression level in the flexor pollicis longus muscle after 8 weeks of combined exercise program according

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to the circadian rhythm and exercise order and the results of one-way ANOVA. One-way ANOVA was used to confirm the difference between groups. The expression level of p-Akt showed a statistically significant difference (F=14.382, p=.001). After performing the post-hoc test, EARG was found to be higher than OCG, MARG, MRAG and ERAG.

Table 61. The result of descriptive statistics and one-way ANOVA for p-Akt/GAPDH ratio in flexor pollicis longus muscle 8 weeks after combined exercise (%)

Group	OCG[1]	MARG[2]	MRAG[3]	EARG[4]	ERAG[5]	Total	*F*	*p*	*Tukey*
p-Akt	0.80±0.06	0.86±0.06	0.89±0.07	1.19±0.19	0.78±0.06	0.90±0.16	14.382	.001	1,2,3,5<4

Mean±standard deviation

p-Akt, phosphorylated Akt; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance- aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group

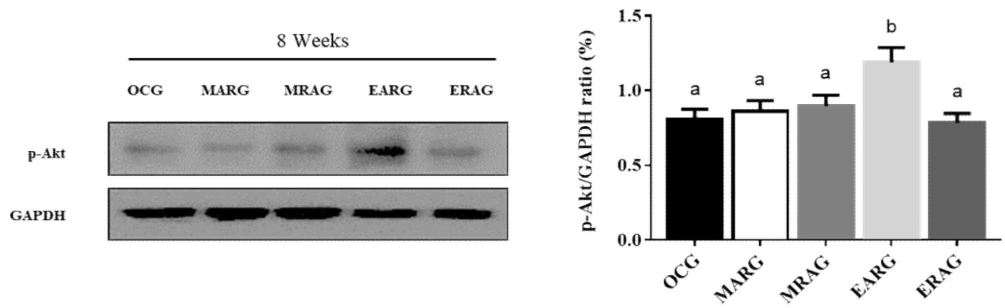

Figure 41. Exercise order and circadian rhythm regulated expression levels of p-Akt in flexor pollicis longus muscle 8 weeks after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group

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(4) Expression of p-ERK1/2 in the flexor pollicis longus muscle after 8 weeks of combined exercise

<Table 62> and <Figure 42> show the results of expression of p-ERK1/2 in the flexor pollicis longus muscle of obese rats after 8 weeks of combined exercise program according to circadian rhythm and exercise order.

<Table 62> shows the descriptive statistics of the p-ERK1/2 expression level in the flexor pollicis longus muscle after 8 weeks of combined exercise program according to the circadian rhythm and exercise order and the results of one-way ANOVA. One-way ANOVA was used to confirm the difference between groups. The expression level of p-ERK1/2 showed a statistically significant difference (F=5.575, p=.013). After performing the post-hoc test, EARG and ERAG was found to be higher than OCG.

Table 62. The result of descriptive statistics and one-way ANOVA for p-ERK1/2/GAPDH ratio in flexor pollicis longus muscle 8 weeks after combined exercise (%)

Group	OCG[1]	MARG[2]	MRAG[3]	EARG[4]	ERAG[5]	Total	*F*	*p*	*Tukey*
p-ERK1/2	0.41±0.05	0.51±0.06	0.50±0.06	0.60±0.08	0.61±0.07	0.55±0.10	5.575	.013	1<4,5

Mean±standard deviation

p-ERK1/2, phosphorylated extracellular signal-regulated kinase 1/2; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance- aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group

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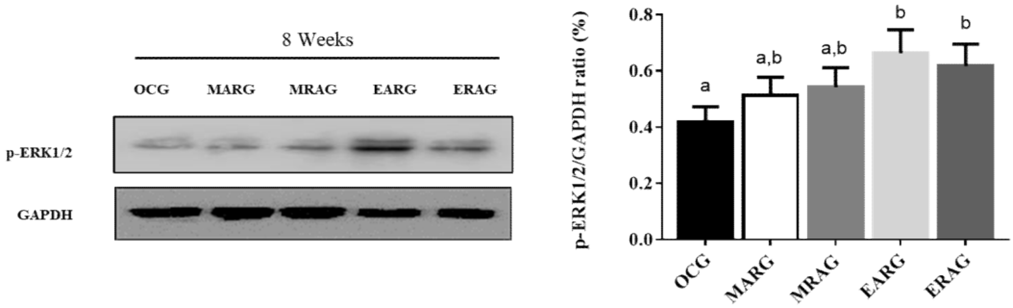

Figure 42. Exercise order and circadian rhythm regulated expression levels of p-ERK1/2 in flexor pollicis longus muscle 8 weeks after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group

(5) Expression of p-mTOR in the flexor pollicis longus muscle after 8 weeks of combined exercise

<Table 63> and <Figure 43> show the results of expression of p-mTOR in the flexor pollicis longus muscle of obese rats after 8 weeks of combined exercise program according to circadian rhythm and exercise order.

<Table 63> shows the descriptive statistics of the p-mTOR expression level in the flexor pollicis longus muscle after 8 weeks of combined exercise program according to the circadian rhythm and exercise order and the results of one-way ANOVA. One-way ANOVA was used to confirm the difference between groups. The expression level of p-mTOR showed a statistically significant difference (F=357.475, p=.001). After performing the post-hoc test, OCG, MARG, MRAG and EARG were found in the order.

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Table 63. The result of descriptive statistics and one-way ANOVA for p-mTOR/GAPDH ratio in flexor pollicis longus muscle 8 weeks after combined exercise (%)

Group	OCG[1]	MARG[2]	MRAG[3]	EARG[4]	ERAG[5]	Total	*F*	*p*	*Tukey*
p-mTOR	0.15±0.01	0.24±0.01	0.44±0.02	0.48±0.02	0.44±0.02	0.35±0.13	357.475	.001	1<2<3<4

Mean±standard deviation

p-mTOR, phosphorylated mammalian target of rapamycin; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group

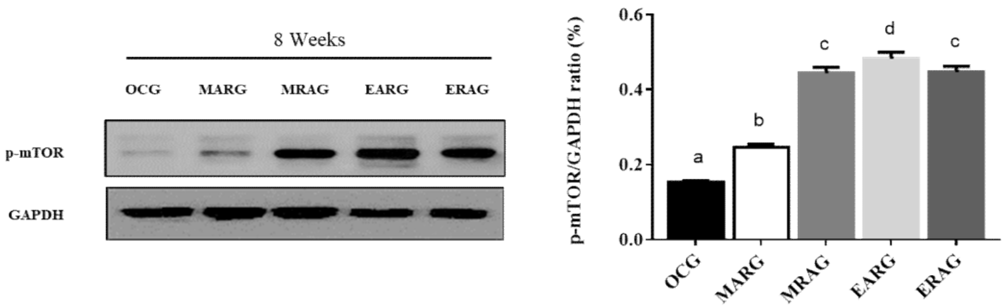

Figure 43. Exercise order and circadian rhythm regulated expression levels of p-mTOR in flexor pollicis longus muscle 8 weeks after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group

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4) Signaling pathway for mitochondrial biogenesis in soleus muscle

(1) Expression of p-AMPK in the soleus muscle after 8 weeks of combined exercise

<Table 64> and <Figure 44> show the results of expression of p-AMPK in the soleus muscle of obese rats after 8 weeks of combined exercise program according to circadian rhythm and exercise order.

<Table 64> shows the descriptive statistics of the p-AMPK expression level in the soleus muscle after 8 weeks of combined exercise program according to the circadian rhythm and exercise order and the results of one-way ANOVA. One-way ANOVA was used to confirm the difference between groups. The expression level of p-AMPK showed a statistically significant difference (F=26.901, p=.001). After performing the post-hoc test, ERAG were found to be higher than OCG, MARG, EARG. In addition, MRAG was found to be higher than ERAG.

Table 64. The result of descriptive statistics and one-way ANOVA for p-AMPK/GAPDH ratio in soleus muscle 8 weeks after combined exercise (%)

Group	OCG[1]	MARG[2]	MRAG[3]	EARG[4]	ERAG[5]	Total	*F*	*p*	*Tukey*
p-AMPK	0.71±0.05	0.81±0.06	1.31±0.10	0.82±0.06	1.04±0.08	0.94±0.23	26.901	.001	1,2,4<5<3

Mean±standard deviation

p-AMPK, phosphorylated AMP-activated protein kinase; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance-aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group

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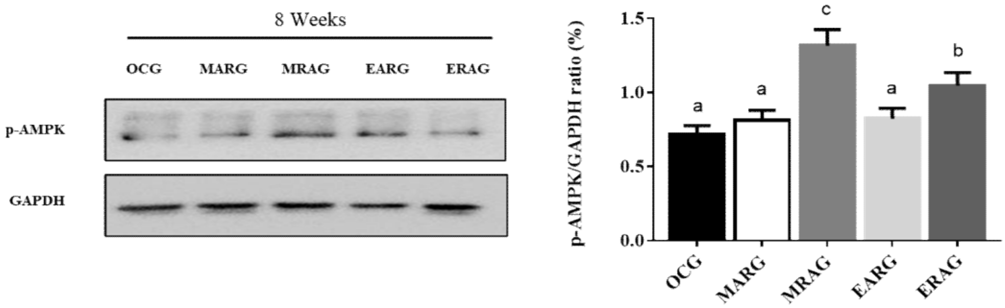

Figure 44. Exercise order and circadian rhythm regulated expression levels of p-AMPK in soleus muscle 8 weeks after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group

(2) Expression of CaMK in the soleus muscle after 8 weeks of combined exercise

<Table 65> and <Figure 45> show the results of expression of CaMK in the soleus muscle of obese rats after 8 weeks of combined exercise program according to circadian rhythm and exercise order.

<Table 65> shows the descriptive statistics of the CaMK expression level in the soleus muscle after 8 weeks of combined exercise program according to the circadian rhythm and exercise order and the results of one-way ANOVA. One-way ANOVA was used to confirm the difference between groups. The expression level of CaMK showed a statistically significant difference (F=33.512, p=.001). After performing the post-hoc test, MARG were found to be higher than OCG, EARG and ERAG. In addition, MRAG was found to be higher than MARG.

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Table 65. The result of descriptive statistics and one-way ANOVA for CaMK/GAPDH ratio in soleus muscle 8 weeks after combined exercise (%)

Group	OCG[1]	MARG[2]	MRAG[3]	EARG[4]	ERAG[5]	Total	*F*	*p*	*Tukey*
CaMK	1.08±0.11	2.17±0.24	2.74±0.30	1.32±0.14	1.44±1.59	1.75±0.65	33.512	.001	1,4,5<2<3

Mean±standard deviation
CaMK, Ca 2+/calmodulin-dependent kinases; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance- aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group

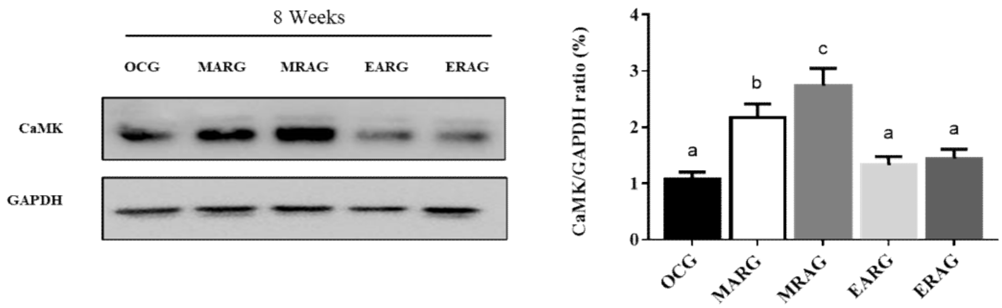

Figure 45. Exercise order and circadian rhythm regulated expression levels of CaMK in soleus muscle 8 weeks after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group

(3) Expression of PGC-1α in the soleus muscle after 8 weeks of combined exercise

<Table 66> and <Figure 46> show the results of expression of PGC-1α in the soleus muscle of obese rats after 8 weeks of combined exercise program according to circadian rhythm and exercise order.

<Table 66> shows the descriptive statistics of the PGC-1α expression level in the soleus muscle after 8 weeks of combined exercise program according to the circadian

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rhythm and exercise order and the results of one-way ANOVA. One-way ANOVA was used to confirm the difference between groups. The expression level of PGC-1α showed a statistically significant difference (F=9.610, p=.002). After performing the post-hoc test, MRAG and EARG were found to be higher than OCG and MARG.

Table 66. The result of descriptive statistics and one-way ANOVA for PGC1-α/GAPDH ratio in soleus muscle 8 weeks after combined exercise (%)

Group	OCG[1]	MARG[2]	MRAG[3]	EARG[4]	ERAG[5]	Total	*F*	*p*	*Tukey*
PGC-1α	1.08±0.17	1.20±0.18	2.13±0.33	1.93±0.35	1.46±0.23	1.56±0.47	9.610	.002	1,2<3,4

Mean±standard deviation

PGC-1α, Peroxisome proliferator-activated receptor-gamma coactivator-1 alpha; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance- aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group

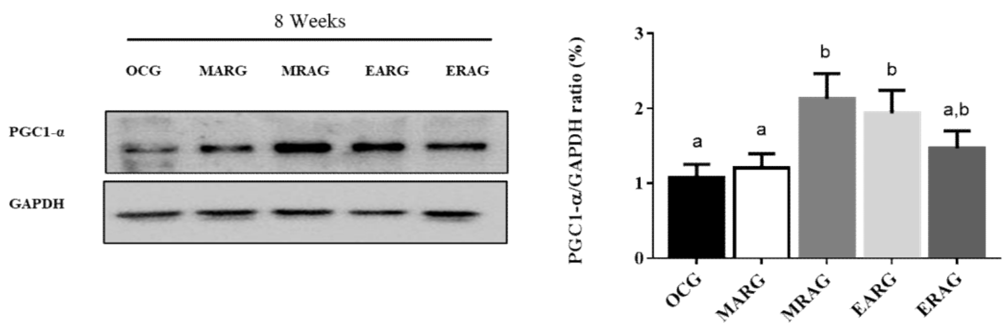

Figure 46. Exercise order and circadian rhythm regulated expression levels of PGC1-α in soleus muscle 8 weeks after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group

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(4) Expression of FNDC5 in the soleus muscle after 8 weeks of combined exercise

<Table 67> and <Figure 47> show the results of expression of FNDC5 in the soleus muscle of obese rats after 8 weeks of combined exercise program according to circadian rhythm and exercise order.

<Table 67> shows the descriptive statistics of the FNDC5 expression level in the soleus muscle after 8 weeks of combined exercise program according to the circadian rhythm and exercise order and the results of one-way ANOVA. One-way ANOVA was used to confirm the difference between groups. The expression level of FNDC5 showed a statistically significant difference (F=.946, p=.036).

Table 67. The result of descriptive statistics and one-way ANOVA for FNDC5/GAPDH ratio in soleus muscle 8 weeks after combined exercise (%)

Group	OCG[1]	MARG[2]	MRAG[3]	EARG[4]	ERAG[5]	Total	*F*	*p*	*Tukey*
FNDC5	1.30±0.13	1.25±0.10	1.16±0.10	1.01±0.08	1.05±0.09	1.15±0.14	.946	.036	

Mean±standard deviation

FNDC5, fibronectin type III domain containing 5; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; OCG[1], obesity control group; MARG[2], aerobic-resistance exercise in the morning group; MRAG[3], resistance- aerobic exercise in the morning group; EARG[4], aerobic-resistance exercise in the evening group; ERAG[5], resistance-aerobic exercise in the evening group

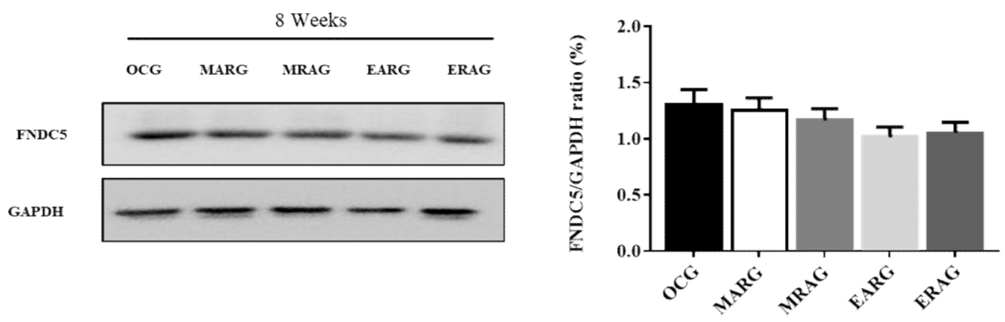

Figure 47. Exercise order and circadian rhythm regulated expression levels of FNDC5 in soleus muscle 8 weeks after combined exercise. OCG, obesity control group; MARG, aerobic-resistance exercise in the morning group; MRAG, resistances-aerobic exercise in the morning group; EARG, aerobic-resistance exercise in the evening group; ERAG, resistance-aerobic exercise in the evening group

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V. Discussion

This study was designed to confirm the effect of combined exercise program and according to the circadian rhythmand exercise order, through clinical and animal experiments. The clinical study analyzed body composition, obesity-related cardiovascular disease risk factors, upper and lower extremity muscle functions, and sleep quality of adult women with obesity before, and 4 and 8 weeks after, participation in a combined exercise program. The animal experiments have been investigated muscle hypertrophy and mitochondrial biogenesis-related protein expression level, and histological analysis of the flexor pollicis longus muscles in rats with obesity, after 8 weeks of combined exercise.

1. Study Ⅰ: Effect of combined exercise according to circadian rhythm and exercise order on body composition, physical fitness, obesity-related cardiovascular disease risk factors, upper and lower extremity muscle functions, and sleep quality in adult women with obesity

Obesity causes diabetes, high blood pressure, cardiovascular disease, and metabolic disease, and hence, must be prevented or managed appropriately. Obesity in women is determined on the basis of body fat percentage (≥30%) and body mass index (≥ 25 kg/m^2), and aerobic exercise and resistance exercise reduce the incidence of obesity-related diseases through decreased body fat and increased muscle mass. Obesity is also closely related to the circadian rhythm, which is changed by food, intake and physical activity. In this study, the body composition (body weight, body fat mass, percent body fat, fat-free mass, and body mass index) of women with obesity was evaluated after 8 weeks of combined exercise participation according to the circadian rhythm and exercise order. There was a significant difference in body

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weight in the interaction between group and period, between periods. And body fat mass in the interaction between group and period, between periods showed a statistically significant difference. Body mass index also showed a statistically significant difference in the interaction between group and period, between periods. However, percent body fat and free-fat mass did not show a statistically significant difference in the interaction effect between group and period. Body weight, body fat mass, and percent body fat did not decrease significantly until 8 weeks of combined exercise but showed a tendency to decrease overall in all exercise groups except for OCG. Exercise appears to be effective in reducing body weight, percent body fat, and body fat mass. Elmahgoub et al. (2009) reported that 10 weeks of combined exercise decreased body fat mass and increased lean mass in adolescents who were overweight and obese. In addition, Ho et al. (2012) showed that 12 weeks of combined exercise was effective in reducing body fat mass, and body fat percentage showed a trend consistent with the study results. Park et al. (2015) showed that 12 weeks of combined exercise of 60–70% 1RM and 40–70% HRR did not reduce fat mass in middle-aged women. Mohebbi & Azizi. (2011) observed that aerobic exercise in the morning and evening effectively reduced fatty acid oxidation and body fat in the evening than in the morning; this was contradictory to the results to this study. In this study, the cause of weight change according to exercise order and circadian rhythm was a decrease in timing due to differences in the characteristics of participants within the group, such as lean obesity and high obesity. Therefore, it was considered that there was no statistically significant difference. In addition, the short period of 8 weeks and the failure to completely control the amount and time of food intake must have affected the change in the circadian rhythm; these are thought to be the main causes for the failure to significantly change the body composition. In the future, additional studies controlling dietary intake and time are required to confirm changes in body composition according to the circadian rhythm and exercise order.

Representative criteria for diagnosing obesity are body fat mass, body mass index,

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and percent body fat. In addition, measurement of waist and hip circumference is very useful as a method to quickly confirm obesity in the field (Sebo et al., 2008). To reduce waist and hip circumferences, aerobic or resistance exercise and combined exercise are required. In addition, considering the circadian rhythm, which affects the fat and muscle metabolic process, will be effective in reducing waist and hip circumference (Donnelly et al., 2003). In this study, waist and hip circumference and waist/hip circumference ratio were measured to confirm the effect on circadian rhythm and exercise order. There was no significant difference in waist circumference in the interaction between group and period, hip circumference in the interaction between group and period, and waist-hip ratio, but the values showed a decreasing trend. Combined exercise performed for 4 months on men with obesity significantly decreased the waist and hip circumference, and waist-hip ratio. In addition, 8 weeks of aerobic exercise and 6 weeks of resistance exercise decreased the waist and hip circumferences in women, partially supporting the results of this study showing a decreasing trend in waist and hip circumferences (Ativie et al., 2018; Mayo et al., 2003; Shaw et al., 2016). This considered to be the main reason that the exercise program in this study, such as leg curls, squats, and lunges, induced hypertrophy of the gluteus maximus and hamstring muscles, and showed a tendency to decrease rather than significantly decrease hip circumference and waist-hip circumference. It is thought that the failure to control the physique characteristics and timing and amount of food intake among participants negatively induced changes in the biological clock of fat cells according to the circadian rhythm, and thus did not significantly reduce the waist and hip circumferences in this study. Therefore, a mechanism to confirm the cell biological change of adipose tissue is required.

Physical strength is necessary for daily life, and improving physical strength helps prevent injuries and obesity, and improves immunity. Strength, muscular endurance, flexibility, and cardiorespiratory endurance are affected by changes in heart rate, body temperature, and hormones according to the circadian rhythm. An increase in body temperature creates an optimal temperature condition that can quickly induce muscle

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contraction. In addition, the exercise order affects recovery from muscle fatigue and must be considered when improving and measuring physical strength. In this study, the effect of circadian rhythm and exercise order on muscular strength, muscular endurance, flexibility, and cardiorespiratory endurance was confirmed. Grip strength and back strength did not show a statistically significant difference in the interaction between groups and period. Sit-ups evaluated muscular endurance, and sit and reach exercises evaluated flexibility. Physical efficiency index was used to evaluate cardiorespiratory endurance and there was no significant difference between group and period. However, all the physical fitness variables showed a considerable increase after 8 weeks, although there was no statistically significant difference from the values measured at 0 week. After 8 weeks of combined exercise, EARG showed significantly higher results than OCG at 8 weeks for sit-ups, and it was found that performing resistance exercise after aerobic exercise in the evening improved muscular endurance. In a study by Yoon et al. (2019), female students performed resistance and aerobic exercises for 12 weeks, and grip strength, back strength, flexibility, and cardiorespiratory endurance were significantly increased. Although not significant, these results support the present results which indicated that basal fitness increased significantly after 8 weeks of combined exercise. A study by Perez-Schindler et al. (2015) reported that performing resistance exercise after aerobic exercise was effective in improving exercise performance. It is the same as the result of the highest increase in muscular endurance (sit-up) in the group that performed resistance exercise after aerobic exercise in this study. Ezagouri et al. (2019) reported that exercise performance was highest in the evening when body temperature and heart rate improved to an appropriate level. This supports the result of EARG showing high muscular endurance in this study and explains that it is effective to perform resistance exercise after aerobic exercise in the evening to improve physical strength. These results are thought to have helped improve muscle endurance by increasing the levels of neurotransmitters and testosterone, along with the expression of mTOR, an indicator of muscular strength and muscle hypertrophy, with higher

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heart rate and body temperature in the afternoon. However, this study only presents the results obtained from clinical trials, and did not explore the changes at the molecular level according to the exercise order and circadian rhythm. Therefore, in Study II, the molecular biological mechanism was studied using animal models.

Obesity has a negative effect on cardiovascular disease. Blood lipids, which are risk factors for cardiovascular disease, are composed of TC, TG, HDL-C, and LDL-C and is affected by exercise and circadian rhythms (Chua et al., 2013). Therefore, in this study, fasting blood glucose and blood cholesterol, which are obesity-related cardiovascular risk factors, were identified, and the effects of circadian rhythm and exercise order on cardiovascular disease risk factors were confirmed. As a result, TC, TG, HDL-C, LDL-C, and FG showed no statistically significant difference in the interaction effect between group and period. Exercise increases blood circulation and HDL-C levels and plays a role in releasing the LDL-C deposited on the blood vessel wall. In a previous study that confirmed the function of such exercise, it was reported that combined exercise decreased TC, TG, and LDL-C and increased HDL-C. And Kelley et al. (2005) reported that aerobic exercise favorably changed blood lipids in people who were overweight or obese, and the results contradicted this study. However, in the study by Ha & So. (2012), 12 weeks of combined exercise did not alter the blood lipid levels, and this finding supports the results of this study, wherein we did not observe changes in blood glucose and blood lipids. In this study, as in the study by Kwon et al. (2020), the blood lipid levels were measured after fasting for 9 hours according to their characteristics. The measured values continued to change depending on the amount of cholesterol ingested; however, the failure to completely control the type and amount of food eaten the previous day could impact the levels of blood lipids. As shown in the study results of Adamovich et al. (2015), the lack of control on the lifestyle and sleep patterns of participants with obesity was associated with the lack of improvements in the obesity-related cardiovascular disease risk factors in this study. Therefore, it is thought that a study that controls the lifestyle, eating habits, and amount of food

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intake is necessary.

Physical strength is a basic necessary for daily life, and improving physical strength helps prevent injuries and obesity, and improves immunity. Strength, muscular endurance, flexibility, and cardiorespiratory endurance are affected by changes in heart rate, body temperature, and hormones according to the circadian rhythm. An increase in body temperature creates an optimal temperature condition that can quickly induce muscle contraction. In addition, the exercise order affects recovery from muscle fatigue and must be considered when improving and measuring physical strength. In this study, the effect of circadian rhythm and exercise order on muscular strength, muscular endurance, flexibility, and cardiorespiratory endurance was confirmed. Grip strength and back strength did not show a statistically significant difference in the interaction between groups and period. Sit-ups to evaluate muscular endurance, sit and reach to evaluate flexibility, and physical efficiency index to evaluate cardiorespiratory endurance showed no significant differences between the group and period.

Muscle function refers to the functional movement of muscles including muscle strength, muscular endurance, and power, and a decrease in muscle function is directly related to injury. The decrease in muscle function is mainly seen in people who are elderly or obese, and it is important to strengthen the core muscles to prevent injuries caused by a decrease in muscle function (Juan-Recio et al., 2018; Lindsay & Horton, 2006). In accordance with the circadian rhythm, the expression level of growth hormone is higher in the afternoon than in the morning, and exercise can play a role in amplifying the expression levels of the growth hormone. Resistance exercise after aerobic exercise is known to induce muscle hypertrophy-related protein expression (Ogasawara et al., 2014). In this study, the upper and lower extremity muscle functions included those of the quadriceps femoris muscle, hamstring, abdominal muscles, erector spinae muscle, latissimus dorsi muscle, and gluteus muscle, which are muscles that originate in the lumbo-pelvic-hip complex (LPHC). FAPT showed a statistically significant difference in the interaction effect

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between group and period. LSAPT and RSAPT did not show a significant difference in the interaction effect between group and period. TFET results showed a significant difference in the interaction effect between the group and period. There were differences observed between the groups; TFET results were improved in the EARG group compared to OCG at 8 weeks. Therefore, performing resistance exercise after aerobic exercise in the evening improves upper extremity muscle function. This is because growth hormones are highly expressed in the evening and p-AMPK expressed by aerobic exercise did not suppress mTOR, an indicator of muscle hypertrophy, when resistance exercise was performed after aerobic exercise. In addition, this exercise program is thought to have increased the TFET in this study as a program that induces core muscle strengthening. Vertical Jump showed that there was no interaction effect between the group and period, but sit to stand test showed a significant difference in the effect of interaction between group and period, and EARG showed improved results compared to OCG at 8 weeks. Weight bearing exercise performed before obesity surgery in patients with severe obesity significantly increased the indicators of physical strength such as FAPT, LSAPT, RSAPT, and performance of modified push-ups (Arman et al., 2021). Aerobic and resistance exercise for 12 weeks improves the muscle function of the upper body of patients with severe obesity, showing partially consistent results with this study (Hernández-Reyes et al., 2019). This is thought to be because, according to the circadian rhythm, an increase in body temperature in the afternoon increases the smooth muscle contraction and the levels of the growth and hypertrophy hormones. In future studies, research using isokinetic equipment is necessary.

Circadian rhythm and sleep-wake cycle are closely related, and exercise affects the regulation of circadian rhythm. The PSQI has been used for many years as a tool to assess sleep quality. The PSQI results according to the circadian rhythm and exercise order showed an interaction between the group and period. As a result of detailed examination between the groups, the groups that performed more exercise than OCG at 4 and 8 weeks showed improved sleep quality. Combined exercise for 12 weeks

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reduced the PSQI score, which is consistent with the results of previous studies that reported the effect of exercise on sleep quality (Taheri & Irandoust, 2018). However, high-intensity exercise at night increases cortisol, which contradicts the results of certain studies (Bonato et al., 2017). The quality of sleep in this study improved regardless of whether the exercise was performed in the morning or evening. These results suggest that exercise increases vitamin D synthesis, and the levels of hormones such as serotonin and the sleep hormone melatonin (Caperuto et al., 2009). However, in this study, changes in sleep hormones such as cortisol and melatonin were not confirmed. Therefore, if we check the changes in sleep-wake hormones according to the circadian rhythm and exercise sequence in the future, it will be possible to clarify the relationship between exercise and sleep quality.

2. Study Ⅱ: Effect of circadian rhythm and exercise order on skeletal muscle hypertrophy and mitochondrial biogenesis in rats with obesity

Obesity not only causes problems in the skeletal muscle metabolic system but is also closely related to disturbance of the circadian clock. The light-activated SCN of the hypothalamus influences peripheral clock regulation in each organ and explains the relationship between circadian rhythm and obesity (Froy, 2010). The most economical way to prevent obesity is exercise, and combined exercise could be a useful therapeutic tool against obesity. Therefore, in this study, 8 weeks of combined exercise designed according to the circadian rhythm and exercise order confirmed the weight change in rats with obesity. As a result, the weight of the rats with obesity showed a significant difference in the interaction effect between the group and period, and it was found that the body weight of all exercise groups was significantly lower than than that of OCG at 8 weeks. Mohebbi & Azizi. (2011) showed that combined exercise when performed in the evening significantly reduced weight, while Alizadeh et al. (2017) demonstrated that aerobic exercise was effective in weight loss. Exercise is thought to promote fatty oxidation by increasing

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mitochondrial biogenesis and function. In this study, combined exercise was found to be effective in weight loss due to an increase in leptin, an appetite suppressing hormone. Therefore, regardless of the circadian rhythm and exercise order, exercise seems to be effective in preventing and controlling obesity by reducing body weight. However, this study failed to continuously determine the dietary intake and appetite-regulating hormones in obese rats; hence, hormones that affect body weight must be considered in the future. The decrease in muscle mass is mainly caused by obesity or aging, and the continuous decrease in muscle mass develops into sarcopenia and is closely related to falls (Landi et al., 2012; Mitchell et al., 2012). Resistance exercise is effective in preventing obesity and sarcopenia in the elderly by increasing muscle mass. Aerobic exercise also induces an increase in satellite cells; hence, exercise seems to have an effect on hypertrophy regardless of the type of exercise performed (Charifi et al., 2003). A typical type II fiber (fast twitch muscle fiber) that confirms muscle hypertrophy has characteristics of type I (slow twitch muscle fiber) with high energy generation and fast muscle contraction speed (Phillips, 2009). For this reason, it is desirable to check the muscle size and protein expression after resistance exercise in type II muscle fibers. Muscle hypertrophy is affected by the circadian rhythm, and BMAL1, a transcription factor that regulates the circadian clock, is involved in muscle hypertrophy (Lipton et al., 2015). However, studies on circulatory rhythm and muscle hypertrophy-related molecular indicators are controversial. Therefore, in this study, a cross-section of the type II muscle fiber in the flexor pollicis longus muscle, was studied after 8 weeks of combined exercise performed according to circadian rhythm and exercise order. The samples were obtained from rats in which obesity was induced using a high fat diet. The samples were analyzed using immunofluorescence staining, and we observed that performing resistance exercise after aerobic exercise in the evening increased the cross-sectional area of the flexor pollicis longus in the order of OCG, ERAG, and EARG. Joanisse et al. (2016) and Kwon et al. (2018) reported that aerobic exercise increased the number of satellite cells in older mice. This finding is consistent with

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the results of this study. Küüsmaa et al. (2016) also showed that type II CSA increased in the evening after morning and evening exercise. This finding supports the fact that the circadian rhythm effect caused the increase in the cross-sectional area of the flexor pollicis longus in the evening exercise group of this study. In addition, considering the study results of Sedliak et al. (2013) who demonstrated that performing exercise in the evening is effective for muscle hypertrophy, it was observed that performing resistance exercise after aerobic exercise in the evening caused the highest increase in CSA of the flexor pollicis longus.

Aerobic and resistance exercise influenced the skeletal muscle metabolism through the following molecular biological signaling pathways. Resistance exercise promoted muscle hypertrophy through the IGF-1, PI3K, Akt, and mTOR signaling pathways, and aerobic exercise induced mitochondrial biogenesis through the AMPK, CaMK, and PGC-1α signaling pathways (Hardie et al., 2012; Kumar et al., 2009; Lantier et al., 2014). In addition, Hayes et al. (2010) reported that the activity of hypertrophy-related signaling pathways was affected by the circadian rhythm. Studies so far have shown that AMPK activated by aerobic exercise after resistance exercise inhibited mTOR and suppressed muscle hypertrophy (Ezagouri et al., 2019; Perez-Schindler et al., 2015). However, studies have also reported contradictory results; therefore, it is necessary to confirm the muscle hypertrophy signaling pathway according to the exercise order and circadian rhythm. In this study, the expression of IGF-1, PI3K, Akt, ERK1/2, and mTOR, which are signal transduction pathway factors related to muscle hypertrophy in rats with obesity, were confirmed using a combined exercise program designed according to the circadian rhythm and exercise order. As a result, IGF-1, PI3K, Akt, ERK1/2, and mTOR all showed the highest expression of hypertrophy-related proteins in the EARG. In previous studies related to exercise order, it was reported that resistance exercise for 12 weeks increased muscle weight, and continuous resistance exercise increased the expression of IGF-1 (Arnarson et al., 2015). Endurance exercise after resistance exercise inhibits the PI3K-Akt-mTOR protein related to hypertrophy through AMPK expression, explaining

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the interference effect on exercise order. The study by Ogasawara et al. (2014) supported the outcome of high signaling pathway protein expression in resistance exercise after aerobic exercise. However, a study that showed an increase in P70S6K after resistance exercise contradicted the results from this study (Shirai et al., 2020). Performing resistance exercise after aerobic exercise is thought to be the main reason that AMPK, which was increased with aerobic exercise, did not affect the inhibition of mTOR, and many research results support the results of this study (Atherton et al., 2005; Dreyer et al., 2006; Frøsig et al., 2004; Nielsen et al., 2003). However, because only the signaling pathways of IGF-1, PI3K, Akt, and mTOR were identified in this study, further studies to confirm changes in p70S6K and 4E-BP1 are required. Looking at previous studies on the circadian rhythm affecting the hypertrophy signaling pathway according to the order of exercise, it was found that resistance exercise performed in the evening increased the muscle hypertrophy index and the width of myotubes of the C2C12 cell line in vitro (Burley et al., 2016). This finding is consistent with the results of the present study. The efficiency of exercise was found to be higher in the evening than in the morning, and the treadmill test results showed significantly higher results in the low- or moderate-intensity exercise experiment in the evening compared to that the morning, supporting the muscle hypertrophy results for the evening exercise in this study (Ezagouri et al., 2019). Resistance exercise induces muscle hypertrophy through the phosphorylation of ERK1/2, and endurance exercise also shows the same pattern (Cao et al., 2007). Previous studies have explained that ERK1/2 phosphorylation, which plays an important role in regulating muscle cell proliferation and differentiation, was activated through exercise. In the evening exercise group of this study, performing resistance exercise after aerobic exercise induced the highest expression of hypertrophy-related protein; this was because when resistance exercise was performed after aerobic exercise, the mTOR interference effect was not deterred according to AMPK, which induced the activity of hypertrophy-related signaling pathways. Muscle hypertrophy is also thought to be caused by the circadian clock markers CLOCK and BMAL1.

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However, because this study did not identify circadian rhythm regulators, it is necessary to further examine the relationship between circadian rhythm and exercise through future studies.

Mitochondria has an important role in metabolism and cellular homeostasis, and the dysfunction of mitochondria in skeletal muscle is closely related to chronic diseases such as diabetes and obesity. In addition, mitochondrial biogenesis is highly dependent on the circadian rhythm, and can be promoted, to an extent, through exercise. In this study, the expression of mitochondrial biogenesis-related proteins according to circadian rhythm and exercise order was confirmed in the soleus muscle. AMPK activity in skeletal muscle is a potent regulator of skeletal muscle metabolism and gene expression as a marker of glucose uptake, fatty acid oxidation, and mitochondrial biogenesis. The expression of p-AMPK in this study was highest in MRAG compared to other groups. A previous study showed that morning aerobic exercise increased mitochondrial biogenesis and glucose and fatty acid oxidation capacity via the AMPK, p38MAPK, and PGC-1α signaling pathways; this was consistent with the results observed in p-AMPK, which exhibited high expression levels in MRAG in this study (Gibala et al., 2009; Ruderman et al., 2003). However, the changes in AMPK according to the exercise order cannot be thoroughly explained, and further information on mitochondrial biogenesis-related mechanisms during morning and evening is lacking. Specific mechanism studies are required to clearly explain the change in the expression of AMPK, a marker related to mitochondrial biogenesis, according to the circadian rhythm. CaMK expression in rat skeletal muscle increases the expression of PGC-1α, a mitochondrial biogenesis regulator, and regulates mitochondrial biogenesis (Wu et al., 2002). The expression of CaMK according to the circadian rhythm and exercise order showed the highest result in MRAG. According to previous studies, aerobic exercise was found to increase the expression of CaMK and improve mitochondrial function (Rose et al., 2007). The study demonstrated that CaMK expression increased even after 80% Vo_2max cycle exercise and anaerobic exercise such as sprint could not explain the

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effect of the order; however, it was found that CaMK expression increased during aerobic exercise and anaerobic exercise regardless of the exercise order (Egan et al., 2010; Serpiello et al., 2011). In this study, the expression of PGC-1α, a key regulator of energy metabolism and mitochondrial biogenesis, was higher in MRAG and EARG than in OCG and MARG. A previous study that performed exhaustion exercise, which involved transition from aerobic to anaerobic exercise, reported that high levels of PGC-1α expression were seen in both moderate-intensity aerobic exercise and exhaustion-level anaerobic exercise. The order of aerobic and anaerobic exercise had an effect on mitochondrial biogenesis, showing the same results as MRAG and EARG in this study (Brandt et al., 2017; Kim et al., 2014). A previous study reported that the expression level of PGC-1α was higher in the evening than in the morning in the C2C12 cell experiment, which could explain why PGC-1α was highly expressed when resistance exercise was performed after aerobic exercise during the evening. Exercise, along with an increase in PGC-1α, synthesizes Irisin, a myokine that delivers blood through muscles, through the activation of FNDC5, a downstream factor in the skeletal muscle cell membrane (Rowe et al., 2014). FNDC5/Irisin is a factor that is known to regulate mitochondrial function, convert white fat into brown fat, and prevent obesity (Boström et al., 2012). In this study, FNDC5 showed a statistically significant difference between the groups; however, there was no difference in the post-test results on whether the expression level of FNDC5 was high according to the exercise order and circadian rhythm. As a result of acute or 21 weeks of combined exercise in men, there was no difference in the expression level of FNDC5 (Pekkala et al., 2013). This is thought to be due to the factors expressed through aerobic and resistance exercise, other than PGC-1α, which are involved in the expression of FNDC5. In addition, PGC-1α could be expressed through morning and evening exercise and might not affect changes in FNDC5 regardless of the circadian rhythm. A study design that is capable of confirming changes in BMAL1, a key regulator of circadian rhythm along with the pathway of Irisin, is required.

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VI. Conclusion

This study aimed to present the optimal exercise order and timing to prevent and control obesity. We investigated the effects of an 8-week combined exercise program, which was designed according to the circadian rhythm and exercise order, on body composition, cardiovascular disease risk factors, upper and lower limb muscle function, and skeletal muscle metabolism.

The following conclusions were made by analyzing the experimental results in this study:

First, combined exercise according to the circadian rhythm and exercise order did not induce changes in body composition in women with obesity. (Study Ⅰ)

Second, combined exercise according to the circadian rhythm and exercise order did not change the physical fitness (grip strength, back strength, flexibility, and cardiorespiratory endurance) of women with obesity, but siginificantly increased the muscular endurance (sit-up). (Study Ⅰ)

Third, combined exercise according to the circadian rhythm and exercise order did not change the cardiovascular disease risk factors (TC, TG, HDL-C, LDL-C) in women with obesity. (Study Ⅰ)

Fourth, 8 weeks of combined exercise according to the circadian rhythm and exercise order favorably affected the upper extremity (TFET) and lower extremity (sit to stand) muscle function in women with obesity. (Study Ⅰ)

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Fifth, combined exercise according to the circadian rhythm and exercise order favorably affected on the increase sleep quality in women with obesity. (Study Ⅰ)

Sixth, combined exercise according to the circadian rhythm and exercise order positively changed the weight change of rats with obesity. (Study Ⅱ)

Seventh, EARG induced the highest change in the cross-sectional area of the flexor pollicis longus muscle in rats with obesity after 8 weeks ofcombined exercise according to the circadian rhythm and exercise order. (Study Ⅱ)

Eighth, EARG induced the highest expression of muscle hypertrophy-related proteins (IGF-1, PI3K, p-Akt, p-mTOR, and p-ERK1/2) in the flexor pollicis longus muscle of rats with obesity, after 8 weeks of combined exercise according to the circadian rhythm and exercise order. (Study Ⅱ)

Ninth, MRAG induced the highest expression of mitochondrial biogenesis related proteins (p-AMPK, CaMK, PGC-1α,) in the soleus muscle of rats with obesity after 8 weeks of combined exercise according to the circadian rhythm and exercise order. (Study Ⅱ)

Tenth, FNDC5, in the soleus muscle was showed significantly difference between groups after 8 weeks of combined exercise according to the circadian rhythm and exercise order.

Therefore, 8 weeks of combined exercise according to the circadian rhythm and exercise order showed that resistance exercise after aerobic exercise in the evening improved the upper and lower extremity muscle functions and sleep quality in women with obesity. In a study on experimental animals, performing resistance exercise after aerobic exercise in the evening activated hypertrophy-related signaling

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pathways. Performing aerobic exercise after resistance exercise in the morning activated mitochondrial biogenesis-related signaling pathways. It was recommended that muscle hypertrophy and physical strength could be improved if resistance exercise was performed after aerobic exercise in the evening. But in this study could not confirm the changes in sleep time, daily food intake, and hormone levels of the participants. In addition, in this study of the molecular pathways, only the results of in vivo experiments using experimental animals are presented. Therefore, further studies are required that can present specific information at the in vitro cellular level.

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국문초록

일주기 리듬과 운동순서가 비만 관련 심혈관질환 위험인자, 상·하지 근기능 및 골격근 대사에 미치는 영향

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본 연구의 목적은 일주기 리듬과 운동순서에 따른 복합운동프로그램이 비만 여성의 비만 관련 심혈관질환 위험인자, 상·하지 근기능과 동물의 골격근 대사에 미치는 영향을 규명하는 것이다. 연구 Ⅰ에서는 비만 여성을 대상으로 임상 연구를 수행하였고, 연구 Ⅱ에서는 비만 쥐를 사용하여 동물실험을 수행하였다.

본 연구 Ⅰ의 목적은 일주기 리듬과 운동순서에 따른 8주간 복합운동이 프로그램이 비만 여성의 신체구성, 비만 관련 심혈관질환 위험요인, 상·하지 근기능 및 수면의 질에 미치는 영향을 규명하는 것이다. 본 연구의 참여를 위해 55명이 모집되었고 대상자 선정 기준에(체지방률 30% 미만, 극심한 아침과 저녁형 인간은 제외함) 부합하지 않은 5명을 제외한 50명이 각 그룹에 무선 배정되었습니다. 실험 참여 도중 개인적인 사정과 운동 참여율 기준(80% 이하)에 따라 6명이 제외되었다. 최종 44명의 비만 여성이 본 연구의 분석에 사용되었다. 본 연구의 집단 구성은 비만 통제 집단(obesity control group, OCG, n=10), 아침에 유산소 운동 후 저항성 운동 집단(aerobic-resistance exercise in the morning group, MARG, n=9), 아침에 저항성 운동 후 유산소 운동 집단(resistance-aerobic exercise in the morning

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group, MRAG, n=8), 저녁에 유산소 운동 후 저항성 운동 집단 (aerobic-resistance exercise in the evening group, EARG, n=9) 그리고 저녁에 저항성 운동 후 유산소 운동 집단(resistance-aerobic exercise in the evening group, ERAG, n=8) 총 5개 집단이다. 본 연구의 복합운동프로그램은 주 3회 8주간 트레드밀 운동(30분)과 웨이트 트레이닝(30분)으로 구성되었다. 일주기 리듬과 운동순서에 따른 복합운동 프로그램의 효과를 알아보기 위해 실험 참여 전, 4주, 8주 후에 신체구성, 기초체력, 비만 관련 심혈관질환 위험인자, 상·하지 근기능 및 수면의 질을 분석하였다. 집단과 시기 간 상호작용을 확인하기 위해 이원반복측정 분산분석을 실시하였으며, 집단 간 차이는 일원 배치 분산분석 후 Scheffe 사후 검정을 실시하였다. 본 연구 결과 복합운동 프로그램은 체중과 신체구성 변화에 통계적으로 유의한 차이는 없었으나, 본 운동 프로그램은 모든 운동 집단에서 긍정적으로 변화하는 경향을 보였다. 근력, 유연성, 심폐지구력은 집단과 시기 간 상호작용 효과는 없었으며, 근지구력은 8주에서 OCG보다 EARG가 유의하게 높았다. 비만 관련 심혈관질환 위험인자는 모든 집단에서 유의한 차이가 없었다. 전면 및 측면 복부 파워 검사를 포함한 상지 근기능은 집단과 시기 간 유의한 차이를 보이지 않았지만, 허리 굴곡 근지구력 검사에서는 8주에서 OCG보다 EARG가 유의하게 높게 나타났다. 앉았다 일어서기 검사 결과는 8주에서 OCG보다 EARG가 유의하게 높았으며, 피치버그 수면의 질 지수는 OCG보다 모든 운동 집단에서 8주에 유의하게 낮았다. 본 연구 결과는 저녁에 유산소 운동 후 저항성 운동순서가 비만 여성의 근지구력, 상·하지 근기능과 같은 체력을 증가시킬 뿐만 아니라, 규칙적인 운동은 운동순서와 시간과는 무관하게 수면의 질을 향상시킬 수 있다는 과학적인 새로운 증거를 제시한다.

두 번째 연구의 목적은 일주기 리듬과 운동순서에 따른 복합운동이 비만 쥐의 장무지굴근과 가자미근에서의 근비대 및 미토콘드리아 생합성 관련 단백질 발현 수준에 미치는 영향을 규명하는 것이다. 본 연구의 집단 구성은 무작위 배정 방법을 통해 비만 통제 집단(obesity control group, OCG, n=6), 아침에 유산소 운동 후 저항성 운동 집단(aerobic-resistance exercise in the morning group, MARG, n=6), 아침에 저항성 운동 후 유산소 운동 집단(resistance-aerobic exercise in the morning group, MRAG, n=6), 저녁에 유산소 운동 후 저항성 운동 집단(aerobic-resistance

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exercise in the evening group, EARG, n=6), 저녁에 저항성 운동 후 유산소 운동 집단(resistance-aerobic exercise in the evening group, ERAG, n=6)으로 구분되었다. 비만 쥐들은 복합운동 프로그램인 트레드밀 운동(30분)과 사다리 오르기 운동(30분)을 주 3회 8주간 실시하였다. 장무지굴근의 횡단면적을 평가하기위해 이중 면역형광염색 기법을 사용하였으며, 근비대 및 미토콘드리아 생합성 관련 단백질의 발현은 웨스턴 블롯 기법을 통해 확인하였다. 집단 간 차이를 확인하기 위해 일원배치 분산분석을 실시한 후 Tukey 사후검정을 실시하였다. 본 연구 결과 장무지굴근의 횡단면적은 OCG보다 MARG, ERAG, EARG에서 유의하게 증가하였으며, 이중 EARG가 가장 높았다. 장무지굴근내 IGF-1, PI3K, p-ERK1/2와 같은 근비대 관련 단백질의 발현 수준은 다른 집단에 비해 EARG가 가장 높았다. EARG는 복합운동 8주 후 다른 집단에 비해 p-Akt, p-mTOR의 발현을 가장 높게 상향조절하였다. 미토콘드리아 생합성 관련 단백질인 p-AMPK, CaMK는 8주간의 복합운동 후 MRAG에서 높은 발현 수준을 보였다. 또한, PGC-1α는 다른 집단보다 EARG와 MRAG에서 높게 발현되었다. 갈색 지방화와 관련된 유전자인 FNDC5는 복합운동 후 집단 간 유의한 차이가 있는 것으로 나타났다. 본 연구 결과는 저녁에 유산소 운동 후 저항성 운동이 근비대에 대한 세포 생물학적 변화를 활성화시키고, 아침에 저항성 운동 후 유산소 운동은 미토콘드리아 생합성의 증가를 통해 유산소성 기능을 조절할 수 있다는 새로운 정보를 제공합니다.

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